



**MEASUREMENT OF SUPRASPINATUS TENDON STRAIN RATIO WITH
SONOELASTOGRAPHY: AN EXPLORATORY STUDY**

by

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Abstract

Purpose

The aim of this study was to measure the strain ratio of supraspinatus tendon, and assess the accuracy of sonoelastography when compared with grey-scale ultrasound in the diagnosis of supraspinatus tendinopathy in patients with shoulder pain. The findings were compared with clinical diagnosis and strain ratio results.

Materials and Methods

The study was undertaken in three phases. In phase 1, 284 asymptomatic supraspinatus tendons of healthy volunteers were assessed by grey-scale ultrasound and sonoelastography to obtain baseline results which included strain ratio.

In phase 2, 204 consecutive patients clinically diagnosed with supraspinatus tendinopathy, results of sonoelastography (index test) were compared with grey-scale ultrasound and clinical diagnosis (reference test). Strain ratio is proposed as a new reference standard and was used to test the accuracy of diagnosis. Supraspinatus tendons abnormalities detectable by grey-scale ultrasound were defined as swelling, hypoechoic or hyperechoic intratendinous lesions, while supraspinatus pathological alterations detectable by sonoelastography were defined as intratendinous tissue softening shown as experimentally proven colour changes and strain ratio values below cut-off value of 4.0 ($p \leq 0.0001$).

In phase 3, intra-observer and inter-observer variability evaluation was done to assess the supraspinatus tendons of healthy volunteers.

Results

The overall mean strain ratio value in healthy supraspinatus tendons was 5.6 (± 1.24 SD). In healthy supraspinatus tendons, 9.9% showed evidence of softening suggesting subclinical tendinopathy which was not evident on grey-scale ultrasound. The correlation (*kappa*) between sonoelastography and grey-scale ultrasound in healthy volunteers was 0.42 showing moderate agreement ($p < 0.001$).

In patients with tendinopathy, the mean strain ratio value was smaller and measured 3.59 (± 5.16 SD) with a significant statistical difference from those without tendinopathy ($p = 0.001$).

When clinical diagnosis was used as the reference standard, sonoelastography showed better accuracy than grey-scale ultrasound {65% (CI: 59 - 70%) compared to 59% (CI: 59 - 70%)}, sensitivity {75% (CI: 60 - 86% compared to 65% (CI: 50 - 78%)} and specificity {63% (CI: 59 - 66%) compared to 57% (CI: 54 - 61%)} ($p < 0.001$).

When strain ratio was used as the reference standard, sonoelastography also showed better accuracy than grey-scale ultrasound {92% (CI: 88 - 94%) compared to 68% (CI: 62 - 72%)}, sensitivity {98% (CI: 92 - 100%) compared to 73% (CI: 58 - 84%)} and specificity {88% (CI: 85 - 90%) compared to 67% (CI: 63 - 69%)} ($p < 0.001$).

There was a statistically good agreement in the symptomatic group between sonoelastography and strain ratio ($k = 0.84$; $p < 0.0005$). The *kappa* measure of agreement between grey-scale ultrasound and sonoelastography was fair with a value of $k = 0.35$ ($p < 0.0005$). There was significant statistical difference in the mean score for the asymptomatic and symptomatic groups ($p = 0.001$).

The *kappa* values for the intra-observer agreement showed very good level of agreement within each observer. Comparison of the inter-rater agreements between the two groups showed good and reproducible *kappa* values of 0.715 (Group 1) and 0.750 (Group 2).

Conclusion

Sonoelastography has been shown to be a valuable imaging modality in the detection of intratendinous tendinopathy. It improved the accuracy, sensitivity and specificity of detection

of tendinopathy when compared with grey-scale ultrasound. Strain ratio colour grading is proposed as new reference standard for supraspinatus tendinopathy.

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Publications and presentations generated in the lifetime of this project

Journal Publications

Ohuegbe, C. I., Ehiwe, E.O., Arogundade, R. (2010). Ultrasound evaluation of Achilles tendinopathy. *Canadian Journal of Medical Imaging and Radiation Sciences*, 41(3), 133-136.

Ohuegbe, C. I., Ehiwe E.O. (2010). A case of Ledderhose disease. *Synergy Imaging & Therapy Practice*, May 2010, 8-9. England.

Oshoja, J., Ohuegbe, C., Ehiwe, E. (2010). The sonographic evaluation and literature review of plantar fasciitis: A case study approach. http://www.theultrasoundforum.com/Dec_10,2010.

Ehiwe, E. O., Ohuegbe, C. I. (2010). Multimodality imaging of the Morton's neuroma: A case study. *Radiography New Zealand* (Accepted for Publication).

Ehiwe, E. O., Ohuegbe, C. I. (2011). Musculoskeletal ultrasound practice: a reflective account of our experience and window of opportunity in Nigeria and Sub-Saharan Africa. *Nigerian Journal of Medical Imaging and Radiation Therapy*, 1(2), 11 – 16.

Ehiwe, E. O., Ohuegbe, C. I. (2011). Magnetic Resonance Imaging of anterior knee bursitis: a case series and review of literature. *Nigerian Journal of Medical Imaging and Radiation Therapy*, 1 (2), 36 - 40.

Published Abstract

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Conference Paper Presentation

Ohuegbe, C., Hussain, B. *Sonoelastography findings in patients with symptomatic supraspinatus tendons and comparison to healthy volunteers*. British Medical Ultrasound Society Conference at The Sage Gateshead United Kingdom in December 9 – 11, 2013.

Ohuegbe, C., Ehiwe, E. *Applications of Sonoelastography: Current Issues and Challenges*. ARN Conference, Minna Nigeria, November 2011.

Ohuegbe, C., Ehiwe, E. *The application of musculoskeletal ultrasound in the differential diagnosis of pathologies in the extremities: an emerging frontier in cross-sectional imaging*. ARN Conference, Minna Nigeria, November 2011.

Ethical Approval

List of Abbreviations

AECC	Anglo European College of Chiropractic
AUC	Area under the ROC curve
BMUS	British Medical Ultrasound Society
CD	Clinical diagnosis
CEO	Common extensors origin
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COCHRANE	Cochrane Reviews are systematic reviews of research in healthcare and health policy that are published in the Cochrane Database of Systematic Reviews.
ECAM	Extended combined autocorrelation method
FNAB	Fine needle aspiration biopsy
FPR	False positive rate
GP	General Practitioner
HiRTE	Hitachi Real-Time Tissue Elastography
ICC	Intraclass correlation coefficient
IQR	Interquartile range
IRRST	Internal Rotation Resistance Stress Test
MEDLINE	The computer-based telephone system of the United States National Library of Medicine that provides rapid linkage to MEDLARS (Medical Literature Analysis and Retrieval System Online)
MeSH	Medical Subject Heading
MHz	Mega Hertz
MRI	Magnetic resonance imaging
MSK	Musculoskeletal
NPV	Negative predictive value
PICO	Patient, intervention, Comparison, and Outcome
PPV	Positive predictive value
QUADAS	A tool for the quality assessment of studies of diagnostic accuracy included in systematic review
ROC Curve	Receiver Operating Characteristic curve
ROC	Receiver operating curve
ROI	Region of interest
RTSE	Real-time sonoelastographic examination
SAB	Subacromial bursa
SASD	Subacromial-subdeltoid
SE	Sonoelastography
SHSSW	School of Health Sciences and Social Work
SR	Strain ratio
SST	Supraspinatus tendon
SSTs	Supraspinatus tendons
STARD	Standard for the Reporting of Diagnostic Accuracy Studies
UKRC	United Kingdom Radiological Congress
US	Ultrasound

Glossary

Autocorrelation – a technique which produces elasticity images with high-speed processing and high accuracy, and achieves a wide dynamic range for strain estimation in tissues. It is possible to acquire measurements in real-time and display them simultaneously on the ultrasound system.

ECAM - a digital processing in sonoelastography that permits quick and accurate analysis and processing of the spectrum reflected echo signal before they are converted to 2D elastographic colour image; this colour image demonstrates the degree of hardness of the scanned tissue. It has the advantage of simple operation that allows the operator to use manual slight compressive force to compress the tissues with the ultrasound linear transducer – a technique simply referred to as ‘freehand technique’

Elasticity – this relates to tissue stiffness; it is defined as the spatial rate of the change of tissue stiffness

Elastogram - the strain image, or elastogram, is an image of relative hardness, since the amount of pressure applied by the transducer will change the amount of tissue displacement and the rate of change in displacement.

Elastography – this is the ultrasonic imaging of elasticity or tissue stiffness; it can be in grey scale or colour where hard tissues are colour-coded as blue and soft tissues are colour-coded as red. On machines using a colour display, low strain values are often displayed as greens or blues and large strain values as yellows or reds. The colours are often overlaid on the B-scan image of the lesion.

Footprint – is the mean maximum mediolateral width of the supraspinatus insertion onto the humerus in the coronal plane.

Rotator cuff tendon – rotator cuff tendons are a group of tendons in the shoulder responsible for movement and rotation, and comprise the supraspinatus, infraspinatus, subscapularis and teres minor tendons. Rotator cuff disease is mainly caused by work overload and this causes damage to the supraspinatus tendon which is the largest tendon of the rotator cuff.

Sonoelastography – is a real-time ultrasound technique that measures tissue elasticity to ascertain the degree of softening and displays it in the form of colour grade and numerical quantification (strain ratio) to make diagnosis.

Spatial resolution – the measure of how closely lines can be resolved in an image is called spatial resolution and it depends on the properties of the system creating the image.

Strain - this is the displacement produced when an object is compressed by external force. Strain is less in hard tissue and more in soft tissue.

Strain ratio – is a quantitative value / ratio / index that mathematically compares the relative stiffness of two areas to improve diagnostic confidence for quantitative assessment.

Supraspinatus tendon - the largest of the four rotator cuff tendons in the shoulder that abducts the shoulder

Tendinopathy - is used for the clinical diagnosis of pain accompanied by impaired performance, and occasionally swelling in the tendon

Tendinitis - corresponds to a histopathological description of tendon impairment associated with an intratendinous inflammation

Tendinosis - is used to describe a histopathological state of degenerative tendon without any inflammatory signs or correlation with clinical symptoms

Tissue strain - the rate of change in the amount of tissue displacement as a function of distance from the transducer is termed "tissue strain" and is displayed as an image.

Ultrasound - is an imaging method that uses high-frequency sound waves to produce relatively precise images of structures within your body; the images produced during an ultrasound examination often provide valuable information for diagnosing and treating a variety of diseases and conditions.

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Dedication

This thesis is dedicated to the great Potentate,
The Lord Almighty, through whom all things are accomplished.

Declaration

I declare that whilst registered for the degree in Doctor of Medical Imaging at the University of Portsmouth, I have not been registered for any other research award at another university. The work undertaken for this degree has not been submitted elsewhere for any other award. The results and conclusions embodied in this thesis are the works the named candidate and have not been submitted for any other academic award. To the best of my knowledge and belief, it contains no material previously published or written by another person, except where due acknowledgement has been made in the text.

Chyke I. Ohuegbe

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Srinivasan & Dubey (2012) sum up the value of this promising imaging technique called sonoelastography:

“The clinical value of sonoelastography of the supraspinatus tendon will only be validated if it is able to offer a substantial advantage in the diagnosis of lesions with poor or indeterminate imaging features (on grey scale US or MR imaging) such as tendinosis where a softening, if reliably detected early, will surely be of clinical significance in the management”.

Chapter 1- Introduction

This chapter begins with a background section which indicates the burden of tendinopathy and its implications. It includes a section on the methodological approach undertaken in this research as well as the rationale for this study. The research questions, aim and objectives of the study as well as a section on the significance and benefits of the study are included in this chapter. It concludes by presenting the ethical consideration which guided this research as well as the synopsis of this thesis.

1.1 Study background

There are empirical evidences which indicate that overuse tendon injuries are a common problem in sports and occupational medicine (Herring & Nilson, 1987; Badcock, Lewis, Hay, McCarney & Croft, 2002). According to Vas *et al.* (2005), they constitute about 50% of all sports injuries. Most tendon injuries involving the Achilles, patellar, rotator cuff, and forearm extensor tendons are also associated with pathologic tendinopathic disease conditions involving the form and structure of the tendons (Rees, Wilson, & Wolman, 2006). Tendinopathy is a pathologic condition affecting many active people and it cuts across age, gender and race (Almekinders, 1998). Some individuals are more susceptible to developing tendinopathy than others who have similar levels of physical activity (Magra & Maffulli, 2008). This disease condition affects the rotator cuff tendons which comprise the supraspinatus, infraspinatus, subscapularis and teres minor tendons.

According to Roquelaure *et al.* (2006), experience gained from clinical practice indicates that degenerative rotator cuff tendon disease is a leading cause of shoulder pain. Literature suggests that it is a common problem in the United Kingdom (UK), Dutch, Brazilian and Spanish populations which has resulted in a high incidence of sick leave among the working population (Herring & Nilson, 1987; Badcock, Lewis, Hay, McCarney & Croft, 2002). In the UK, musculoskeletal disorders accounted for 9.9 million days of sick leave and lost revenue in 2006. 4.2 million (42%) of this were related to the upper limb and neck area (Jones, Britain & Britain, 1998; Linsell *et al.*, 2006). Shoulder pain preponderance within populations in the UK is estimated to be between 11.7%

and 16% (Badcock, Lewis, Hay, McCarney, & Croft, 2002; Rees, Wilson & Wolman, 2006), reaching 21% in geriatric hospital populations (Rees, Wilson & Wolman, 2006). A later study (Lewis, 2009) showed that the prevalence of shoulder disorder in the UK ranges from 30% of people experiencing shoulder pain at some stage in their lives up to 50% of the population that experience at least one episode of shoulder pain in a year. In addition, about 54% of victims report continuous symptoms after 3 years.

According to Kainberger *et al.* (1996) and Nallamshetty *et al.* (2005), prior to the advent of sonoelastography, the other methods of investigating rotator cuff disease include ultrasound imaging, magnetic resonance imaging (MRI) and computerized tomography (CT) arthrography. These modalities have associated limitations which make them unable to assess the mechanical properties of the tendons. MRI is the gold standard for diagnosis of shoulder pathology (Adams, Schoofield & Burkhart, 2010). It has limited availability to everyone. It is expensive and shows poorer sensitivity than ultrasound in the diagnosis of (Achilles) tendinopathy (De Zordo *et al.*, 2009a). A study that compared the sensitivity and specificity of ultrasound with MRI found both modalities demonstrating comparable sensitivity and accuracy in the diagnosis of supraspinatus tendon tears (Khan *et al.*, 2003). A summary receiver operating characteristics (ROC) curves for MR arthrography, MRI, and ultrasound for all rotator cuff tears showed the area under curve is greatest for MR arthrography (0.935). This is followed by ultrasound (0.889) and then MRI (0.878). There are no significant differences in either sensitivity or specificity between MRI and ultrasound in the diagnosis of partial- or full-thickness rotator cuff tears ($p > 0.05$) (de Jesus *et al.*, 2009). These other modalities lack the capability to demonstrate early tissue changes or alterations that may suggest tendon pathology as diagnosis is based on certain imaging criteria – ultrasonic echogenicities rather than mechanical properties (Nallamshetty *et al.*, 2005). It is in the light of this that this study was undertaken to explore the possibility of using sonoelastography in the assessment of tendinopathy as a disease condition in the supraspinatus tendon of the shoulder.

Following on from the above, it is important to also note that real-time ultrasound imaging of the supraspinatus tendon demonstrates good sensitivity in the

diagnosis of tendon injury and pathologies. However, some subtle changes in tendon appearance remain poorly delineated by grey-scale ultrasound (Nallamshetty *et al.*, 2005), and therefore there is need for a more sensitive method of demonstrating these changes. This gap in tendon imaging is what this study will evaluate using sonoelastography, a modality that has the capability to estimate tissue alteration (softening or hardening) and demonstrate it as colour change and quantitative value for diagnosis.

Sonoelastography is an application that involves visual soft tissue colour changes and quantitative analyses of tissue elasticity in terms of strain ratio. In an elastographic image (elastogram), hard tissue appears as blue and soft tissue appears red, while yellow and green show increasing tissue hardness. These colours correspond to the relative hardness of the tissues in the elastogram which is a measure of its elasticity.

Changes in the tissue elasticity can cause colour alteration in an elastogram (Frey, 2003). The ability to compress tissues easily can be used to estimate tissue softening (Khoury & Cardinal, 2009) and can serve as a useful tool to characterize an intratendinous lesion or peritendinous involvement in the supraspinatus tendon (De Zordo *et al.*, 2009a). In tendinopathy, the tendon becomes progressively softer than its hard consistency. The soft feature of the tendon is depicted as a medium-to-soft on the colour map and shows as yellow-to-red in the elastogram (as opposed to usual hard structure which shows as predominant blue and patches of green in the elastogram). This characteristic feature, which is not available in grey-scale ultrasound or MRI, will be used in this research to assess the presence of tendinopathy in this study.

A relevant study upon which this study is predicated was a pilot study by Hussain (2008). It investigated the potential of sonoelastography on supraspinatus tendon among twenty five supraspinatus tendons of normal volunteers. The author reported that sonoelastography has the potential to show subtle changes that are not readily demonstrated by conventional ultrasound (Hussain, 2008). It is in the light of this that this current research examined a larger population of normal volunteers to establish a credible baseline values of strain ratios. With the knowledge of baseline values of normal tendons, patients

with clinical indications of supraspinatus tendinopathy were evaluated to assess the accuracy of sonoelastography in diagnosing supraspinatus tendinopathy. A ROC curve was produced from the strain ratio values to produce a cut-off value of 4.0 that was used as a reference standard in assessing diagnostic accuracy

As part of the background review undertaken in this study which involved examining the shoulder, relevant literature on the effect of side dominance with respect to sonoelastography were explored and considered. While it was noted that the effect of side dominance has not been fully investigated in this area, a study by Malanga *et al.* (2012) was considered useful. The authors explored, using grey scale ultrasound, the disparity in supraspinatus tendon in dominant and non-dominant shoulders. The results showed that the dominant side for right-handed pitchers displayed increased tendon thickness compared to the non-dominant side. In another quantitative study of healthy subjects, the cross-sectional area (CSA) of the supraspinatus muscle was found to be larger on the dominant side ($7.07 \pm 0.94 \text{ cm}^2$) than on the contralateral side ($6.91 \pm 0.90 \text{ cm}^2$) and progressively decreased with ageing (Katayose and Magee, 2001).

However, a previous study using direct measurement on cadavers reported value for the CSA of 5.21 ± 1.76 and did not distinguish between right and left sides (Veeger, Van der Helm, Van der Woude, Pronk, Rozendahl, 1991). Poppen & Walker (1978) also found that the value for CSA on cadavers was 6.21 cm and did not distinguish between right and left sides. Majority of the published literature on sonoelastography did not consider the effect of side dominance and if it had any impact on their findings. It is in the light of this that this area of concern was not considered relevant to this research on tendinopathy of the supraspinatus.

1.2 Methodological approach in this research

A diagnostic research design was used to undertake this research study in three phases. Phase 1 assessed healthy supraspinatus tendons with grey-scale ultrasound and sonoelastography to obtain baseline measurements. Phase 2 evaluated shoulder pain patients with confirmed clinical indications of tendinopathy comparing grey-scale ultrasound and sonoelastography. Phase 3

assessed the intra-observer and inter-observer reliability test of normal supraspinatus tendons of two different groups.

Phase 1: a sample size of 284 normal volunteer supraspinatus tendons were established referred to as “the asymptomatic group”. This group was investigated using grey-scale ultrasound and sonoelastography, and the strain ratio was measured to establish baseline measurements. The results of this stage presented grey-scale ultrasound images and sonoelastograms with strain ratio values.

Phase 2: a sample size of 204 supraspinatus tendons of patients with clinical diagnosis of tendinopathy were established referred to as “the symptomatic group”. They were investigated using grey-scale ultrasound and sonoelastography to compare their diagnostic accuracy of detecting tendinopathy. The results of the group were compared to that of Study 1 group. Grey-scale ultrasound and clinical diagnosis were used as reference standard. Strain ratio cut-off value of 4.0 was also used as a new reference standard.

Phase 3: assessed the strain ratio values of intra-observer and inter-observer variability and reproducibility in normal “asymptomatic” supraspinatus tendons. This was carried out in two groups: group 1 assessed 50 supraspinatus tendons between Observers 1 and 2; and group 2 assessed 40 supraspinatus tendons between Observers 1 and 3 recruited from Phase 1 group.

1.3 Rationale for this study

The following points indicated below formed the stimuli which motivated the need for this study:

1. As a clinician in practice who regularly examines patients' shoulders using grey scale ultrasound, I felt there was a need for a more definite diagnosis of supraspinatus tendinopathy as this was a common finding in all my patients. This point is significant in view of the points already indicated in the background section about lost revenue resulting from man hours lost due to sick leave and the working population. Patients presenting with shoulder pains prompted this study. Supraspinatus tendinopathy is a relatively common and disabling

condition, and therefore requires early and accurate diagnosis. Many soft tissues can share similar ultrasound echogenicities but may have different mechanical properties that can be used to clearly visualize normal anatomy and delineate diseased tissues. This limitation of grey-scale ultrasound can preclude early diagnosis and increase patients' waiting time and delay treatment. Investigating the role of a new and alternative technique like sonoelastography was necessary to see if this can improve patient management.

2. Findings of this research could be useful in the detection of subclinical disease in tendons and aid improving the detection of tissue softening representing tendinopathy. This could add prognostic information like predicting tendinopathy at an early stage and preventing further disease progression.

3. It was expected that the results of this research would have the capacity to influence practice and improve patient management pathway. Sonoelastography displays colour and strain values to demonstrate tissue alteration. The early detection using quantitative method will give definitive diagnosis with the aim of improving patient care. This study aims to incorporate sonoelastography into the protocol for imaging tendon pathology.

1.4 Research questions

1. Is sonoelastography more accurate than grey scale ultrasound in the diagnosis of the supraspinatus tendinopathy in patients with shoulder pain?
2. Is strain ratio, a component of sonoelastography, useful in measuring supraspinatus tendon elasticity?

1.5 Aim of the study

The aim of this study was to measure the strain ratio of supraspinatus tendons and assess the accuracy of sonoelastography when compared with grey-scale ultrasound in the diagnosis of supraspinatus tendinopathy in patients with shoulder pain. The findings were compared with those obtained at clinical diagnosis and strain ratio.

1.6 Study objectives

The four key objectives for this research are:

1. To conduct a comprehensive and critical reviews of literature review to ascertain the efficacy of previous studies using sonoelastography.
2. To establish sample groups of supraspinatus tendons of normal adult volunteers referred to as “the asymptomatic group” and patients with clinical signs of supraspinatus tendinopathy referred to as “the symptomatic group”; both groups were investigated using grey-scale ultrasound and sonoelastography to establish baseline strain ratio measurements and estimate diagnostic accuracy.
3. To compare the diagnostic accuracy of grey-scale ultrasound and sonoelastography in the assessment of tendinopathy using clinical diagnosis and strain ratio as reference standards, and to establish a new reference standard in the form strain ratio.
4. To assess the intra-observer and inter-observer variability and reproducibility in normal “asymptomatic” supraspinatus tendons.

1.7 Significance and benefits of the study

1. The outcome of this study will inform the potential for sonoelastography to define tissue changes earlier in damaged tendons leading to early and more definitive diagnosis.
2. The result of this study will lead to early diagnosis of tendinopathy compared to grey-scale ultrasound, and subsequently reduce the incidence of work-related sick leave (Linsell et al, 2006; Matsudaira, Hara, Arisaka, & Isomura, 2010). This will impact positively on the health economy (Rees, Wilson & Wolman, 2006).
3. The results of this research will be important as it proposes a new reference standard, strain ratio, for diagnosis of tendinopathy in addition to existing ones like ultrasound, MRI, clinical diagnosis.
4. The study will influence practice positively by being used in clinical settings for the interpretation of sports injuries, orthopaedic diseases,

rheumatology and evaluation of the repair process. This would improve quality of life (Rees, Wilson & Wolman, 2006).

1.8 Ethical Consideration

Before the commencement of this research, an application for its assessment for ethical review was submitted to the AECC Research Ethics Committee (AECC REC). The research site was the Centre for Ultrasound Studies in the AECC under the mentorship of Dr Budgie Hussain. After consideration, an approval was granted to the research protocols as shown on the ethical approval page. The protocol for this research and full ethical approval were given by the School of Health Sciences and Social Work (SHSSW) of the University of Portsmouth.

Standard ethical principles of research and clinical governance which ensured that this project met minimum standards were considered and employed. These helped to guide and inform all the decisions and actions undertaken during the lifetime of this project. Conscious efforts were made to guarantee the dignity, rights, safety and well-being of all the research participants. The risk of unforeseen hazards to the participants and the researcher were considered and avoided by undertaking the data collection in the AECC Ultrasound department which is a safe and convenient environment should there be need for emergencies. Confidentiality and anonymity were ensured with each participant given a code name such that their personal identifiable details were preserved and kept secret. Only the researcher and the supervisory team had access to these names.

In the same vein, the questions and explanations in the participants' information sheet and consent form of the study were carefully considered and worded with the support from my supervisory team bearing in mind the principles of non-maleficence, beneficence, autonomy and justice. These helped to ensure that the rights of the participants were respected. All these were promised and ensured in a participant information sheet for all the participants. The following steps were taken to ensure that informed consent, confidentiality, beneficence and reduced risk of participation were guaranteed.

1.8.1 Informed Consent

The participants were given a clear explanation of the study aim and objectives, the implications, benefits or consequences of taking part in this study in participant information letter. This was done by explaining to them the processes involved and what was expected of them as indicated by Mays & Pope, (2000). Efforts were made to explain and get them carried along in contributing to the research as well as on how to get the final outcomes of the project.

1.8.2 Confidentiality & Anonymity

Participant confidentiality was assured and anonymity provided to all the participants. The normal volunteers were given coded names by which they were referred to throughout the lifetime of the project. All the patients' individual names were separated from the research centre data and stored separately with coded names. All the data collected from all the participants were password encrypted and saved in memory drive and safely locked away with access granted only to the researcher.

1.8.3 Beneficence

In line with the principle of beneficence, the participants were told that although they would not benefit directly from participating in this project, their contributions could help influence health care delivery, improve health education measures and improve management of tendinopathy and shoulder pain. They were made to understand the results of the research would reflect in all publications as a result of this project.

1.8.4 Risks of Participation

Prior to undertaking this research, the possibility of this exercise creating uncomfortable emotions was explained to the participants especially the normal volunteers before the project started. Counsel and support were also available. Any participant was free to withdraw from the research at any point without giving a reason. Declining did not in any way affect the investigation and the results.

1.9 Synopsis of this Thesis

A summary of the reference tests used in the study are described below:

1. Clinical diagnosis – the following tests were used to confirm the presence of supraspinatus tendinopathy: Jobe's "supraspinatus test", the Neer sign, the Hawkins' test and the Internal Rotation Resistance Stress Test – IRRST.
2. Strain ratio - a ROC curve analysis was constructed using the Youden's test. An optimum cut-off strain ratio value of 4.0 was used to distinguish between normal and abnormal (tendinopathic) tendons if the strain ratio value was above or below 4.0 respectively.

The thesis consists of seven chapters.

Chapter one is the background of the study and it details the introduction to sonoelastography technique. The chapter addresses the research question, aim and objectives of the study, the rationale of the study and possible benefits of the study.

Chapter two presents relevant literatures that were reviewed on sonoelastography, its applications in musculoskeletal pathologies and limitations of this technique. A discussion on rotator cuff tendons, the nature of tendinopathy as well as tendon disease aetiology and pathophysiology are also presented in this chapter.

Chapter three presents the first phase in this research project. This phase evaluated the elasticity of supraspinatus tendon using grey-scale ultrasound and sonoelastography in normal volunteers. It presents a report of strain ratio values in male, female and combined mean. These results were used to establish baseline data for the next phase of the research.

Chapter four presents the second phase of the study for the symptomatic patients using quantitative diagnostic research design. This enabled the study to determine the presence or absence of supraspinatus tendinopathy in order to assess the effectiveness of sonoelastography in estimating diagnostic accuracy. The study was based on three colour grading sonoelastographic patterns seen in

tendons. Grade 1 pattern is the pattern for normal tendon and shows a characteristic blue-green pattern which is an indication of hard tissue appearance. Grade 2 pattern shows presence of yellow colouration within the tendon to indicate mild tendon softening. Grade 3 colour pattern shows evidence of red colouration within the tendon. The presence of grades 2 and 3 patterns are consistent with tissue softening or tendon pathology. The study measured the strain ratio of supraspinatus tendon and assessed the accuracy of sonoelastography when compared with ultrasound in the diagnosis of supraspinatus tendinopathy in patients with shoulder pain. The findings were compared with those obtained at clinical examination and strain ratio.

Chapter five presents the third phase of the study. It evaluated intra-observer and inter-observer variability and reproducibility in normal “asymptomatic” supraspinatus tendons using two different groups of normal volunteers

Chapter six presents the conclusion of this study and discusses the implication of the findings, summary of achieved objectives and study contributions. It concludes by emphasizing the recommendations and areas for further research.

Chapter seven presents my reflection throughout this period of training in this professional doctorate programme. The chapter explores the gains from different learning theories that were taught. It shows how the learnt theories and research methodologies were the necessary tools that were required to set the scene to accomplishing the research work and writing the thesis for an eventual accomplishment of an acceptable project. It concludes with a reflection on my own learning and personal development.

1.10 Summary

There are clinical challenges associated with any new imaging technique as none is flawless including sonoelastography. The challenges include ascertaining the exact cut-off to distinguish normal and tendinopathic tissues, standardization of elastograms, long learning curves, operator dependency, quantification and reproducibility which remain to be made ideal.

Degeneration of the supraspinatus tendon is a relatively common disease condition which impacts on patients' quality of life. Literature shows that measuring elasticity can aid in accurate diagnosis of tendinopathy and, once diagnosed, treatment can take place. Ultrasound and MRI possess a major limitation such as their inability to measure tissue compressibility, which makes it difficult to demonstrate the different mechanical properties that can be used to clearly visualize normal anatomy and define diseased tendon tissues. "Visual resolution" can be defined for the purpose of this thesis as the amount of detail that can be distinguished in an image by the human eye. Measuring shoulder tendon elasticity using sonoelastography will provide better accuracy because of its increased visual resolution, employment of quantitative values and colour map to improve detection of pathology. The current study evaluated sonoelastography in the assessment of the supraspinatus tendon in healthy volunteers, and in patients with clinical diagnosis of supraspinatus tendinopathy. The findings were compared with grey-scale ultrasound and strain ratio.

The next chapter presents the literature reviewed in the course of this research study.

Chapter 2 – Literature Review

2.0 Introduction

The chapter has two sections. An account of the literature review strategy indicating the process of how relevant research, publications and grey literature were identified and reviewed is briefly presented in section one.

Section two starts with a review of the aetiology of supraspinatus tendinopathy with emphasis on pathophysiologic conditions which influence this condition. A critique of the mechanism of pain and its relationship to tendinopathy has been discussed. The role of clinical diagnosis and imaging in tendinopathy are further evaluated while the outcome measures of sonoelastography and its influence in demonstrating change in practice for improved patient management were also reviewed in this chapter. The chapter concludes by evaluating a synopsis of current evidences on sonoelastography, the effect of side dominance and limitations of sonoelastography. It identified gaps in knowledge that prompted further research on this subject.

2.1 Section One

2.1.1 Literature Review Strategy

A literature review of the following databases was done: CINAHL, MEDLINE, EMBASE, and the Cochrane Library. The search included literature published between 1991 and 2014. The first major publication on elastography was published by Ophir *et al.*, (1991). A range of keywords and search terms was utilised using these MeSH (Medical Subject Heading): tendinopathy, pathophysiology, rotator cuff, shoulder pain, elasticity imaging techniques, elastography, sonoelastography, tendons, musculoskeletal, real-time, ultrasonography, ultrasonics, ultrasound, supraspinatus, tendons, magnetic resonance imaging, strain ratio, increased accuracy, detection and diagnosis.

A wide range of grey literature of published and unpublished references was searched to identify articles and reports (e.g. as early as 1934 and 1973). Websites for musculoskeletal imaging like the Hitachi ultrasound publications on

sonoelastographic investigation were assessed for information. A hand search for key journals was also undertaken.

Inclusion criteria

The following criteria were used to select papers reviewed for this study:

- Relate to musculoskeletal imaging like ultrasound and MRI;
- Relate to elasticity and sonoelastographic imaging of tendons, muscles, breast, thyroid, testes;
- Relate to diagnostic tests;
- Relate to aetiology and pathophysiology of tendinopathy.

Exclusion criteria

- Papers not reported in English were excluded and not considered as there was no access to a translation service and it would have proved expensive to have one.

Search Outcome

Using the PICO (patient, intervention, comparison, and outcome) as a qualification search strategy, reference titles were retrieved by assessing the effects of (intervention or comparison) for (health problem) in (types of people, disease or problem), and appropriate healthcare setting and their outcomes.

The CASP tool for diagnostic study (Appendix A) and STARD checklist for reporting of diagnostic study (Appendix B) were models used to grade the quality of the papers and articles to ensure rigour in the review process. The Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS 2) tool was used to critique the quality of each paper (see Appendix C). Papers which addressed a clear question, had a clear set of aims and had the most appropriate-strongest evidence were reviewed. A total of 8,491 references were retrieved while 8,311 were rejected on a review of their titles while 180 abstracts were screened. From the screening, 68 were rejected at abstract level while 112 full papers were initially accepted. A total of 85 papers were critiqued while 27 were finally rejected (Appendix H) based on CASP and STARD criteria.

2.2 Section Two

2.2.1 Relationship between aetiology, pathophysiology and risk factors of tendinopathy

In an attempt to understand the aetiology, pathophysiology and risk factors of tendinopathy which are important in assessing the accuracy of sonoelastography in the diagnosis of supraspinatus tendinopathy, the studies of Nirschl and Ashman (2003), Jarvinen *et al.* (2005) and Fredberg and Stengaard-Pedersen (2008) were found relevant. They all agreed that the aetiology of tendinopathy could be both intrinsic and extrinsic, or a combination of both. In line with this, Rees, Wilson & Wolfman (2006) evaluated three theories to support the aetiology of tendinopathy. These theories are the mechanical, vascular and neural theories. Each of these theories is briefly discussed below.

In relation to aetiology of tendinopathy, the mechanical theory suggests that repeated loading within the normal physiological stress range of a tendon can cause fatigue. This eventually leads to tendon failure. When tendons experience high strain, this may lead to microscopic degeneration within the tendon especially with repeated and/or prolonged stressing. According to Curwin (1998) and Wren, Lindsey, Beaupre & Cater (2003), this progresses to a symptomatic tendon with distorted mechanical properties as a result of repeated microtrauma. This theory explains how chronic repetitive damage to tendons could accumulate over time and perhaps why tendinopathy would be degenerative rather than inflammatory in nature. It is in the light of this that this theory is consistent with increased incidence of tendinopathy with age and in the active population (Rees, Wilson & Wolman, 2006).

A review of the pathophysiology of tendinopathy and vascular theory indicates that as tendons become metabolically active and require a vascular supply, there is resultant degeneration when there is a compromise in blood supply. According to Rees, Wilson & Wolman (2006), this could be due to overuse and may cause damage at both the micro- and the macro-vasculature. However, Fenwick, Hazleman & Riley (2002) argued that certain tendons are susceptible to vascular compromise (Ling, Chen & Wan, 1990), the Achilles (Ahmed *et al.*, 1998) and

the tibialis posterior (Frey, Shereff & Greenidge, 1990). However, this theory remains debateable as Åstrom & Westlin (1994) advocated the presence of uniform blood flow in the Achilles with the exception of its distal insertion.

The neural theory supports the fact that tendons are innervated according to Andres, Von Düring & Schmidt (1985), Józsa *et al.* (1993) and Hart, Frank & Bray (1995), and there exists the likelihood of mast cell degranulation and release of mediators (Hart, Frank & Bray, 1995) which are neurally mediated. This theory agrees that chronic tendon overuse could result in excessive neural stimulation and consequent mast cell degranulation. In support of this theory, a study by Gotoh *et al.*, (1998) has shown that increased levels of these mediators were found in rotator cuff tendinopathy. Similarly, Lewis (2009) agrees in his paper, which studied rotator cuff tendinopathy and subacromial impingement syndrome that the large subacromial bursa is innervated and appears to have a vital role in the presentation of pain in the shoulder. In view of the above, this review sought to examine if and how these theories impact tendon degeneration with particular reference to the supraspinatus tendon.

Impact of these theories on degeneration of the supraspinatus tendon

In a critical review of tendon degeneration with particular reference to the rotator cuff by Rees and colleagues, the authors considered how the different theories could be used to explain the degeneration of the rotator cuff and supraspinatus tendon (Rees, Wamuo, Jan & Gibson, 2004). They noted that rotator cuff degeneration and the size of cuff tears increase with age (Hijioka, Suzuki, Nakamura & Hojo, 1993; Sher *et al.*, 1995). In elderly patients, the supraspinatus tendon was found to be susceptible to degenerative change (Rees, Wamuo, Jan & Gibson, 2004). Although the relationship between ageing and degeneration has not been well established and may be controversial, several theories have been offered to account for this relationship (Mehta, Gimbel & Soslowsky, 2003).

In a review of rotator cuff rupture involving the supraspinatus tendon and other lesions by Codman (1934), the author suggested that the critical zone which is an avascular area close to the point of insertion of the supraspinatus tendon was thought to be affected by increase with age and the position of the shoulder. This

opinion was also supported by Rathbun & Macnab, 1970; Ling, Chen & Wan, 1990; Rees, Wilson & Wolfman, 2006.

On the contrary, another theory by Brooks, Revell & Heatley (1992) suggested that supraspinatus and infraspinatus tendons have an area of vascularity near to the humeral insertion thereby signifying that other factors than vascularity are implicated. Carr & Harvey (2005) later claimed that hypovascularity could be a consequence of injury and not the cause.

A different theory by Nicholson, Goodman, Flatow & Bigliani (1996) based on anatomical variation attributed acromial morphology to supraspinatus tendinopathy. The theory claims that acromial shape relates to different degrees of incidence of cuff tendinopathy and tears. However, the value of this claim has been queried because of poor inter-observer variability in identifying acromion type (Zuckerman, Kummer, Cuomo & Greller, 1997) and the fact that acromion type of pathology may be age-related (Wang & Shapiro, 1997). Impingement of the rotator cuff, especially the supraspinatus tendon, was proposed by Neer (1983) as fundamental to their degeneration. He argued that this happens when the anterior margin of the acromion 'impinges' on the supraspinatus tendon during forward flexion. This impingement can be relieved by decompression surgical procedure of the subacromial space (Rees, Wilson & Wolfman, 2006). In line with the above findings, this review noted that it was unclear what the true impact of impingement and vascular theory are on the high incidence of supraspinatus pathology as indicated by Luo *et al.*, (1998) and Rees, Wilson & Wolfman (2006).

In view of these controversies, though the role of inflammation is still debated by several authors (Sharma & Maffulli, 2005; Riley, 2008; Millar, Wei, Molloy, Bonar & Murrell, 2009), studies in animal and human tissues support both the mechanical theory and the concept that inflammation plays a role in the aetiology of acute tendinopathy while a degenerative process often supersedes this (Rees, Wilson & Wolman, 2006). Studies by other authors have shown that an inflammatory process may be related to the development of chronic tendinopathies (Fredberg & Stengaard-Pedersen, 2008; Millar, Wei, Molloy,

Bonar & Murrell, 2009). However, other authors believe that the nonexistence of inflammatory cells in or around the degenerate lesion does not indicate that inflammatory mediators are not implicated in tendinopathies (Rees, Wilson & Wolman, 2006; Riley 2008; Millar, Wei, Molloy, Bonar & Murrell, 2009).

This review also found that a common site for calcific tendinopathy is the supraspinatus tendon. Uhthoff and colleagues proposed pathogenesis of calcific tendinopathy which include calcification secondary to tendon degeneration and chondrogenic metaplasia of the tendon have been proposed (Uhthoff, 1975; Uhthoff, Sarkar & Maynard, 1976). Their report further suggested a cell-mediated process, which is basically self-limiting. In another report, Evans, Benjamin & Pemberton (1991) maintained that maximum amount of calcified tissue occurs at the tendon insertion and relate to the degree of force transmitted through the tendon. According to Cluett (2008) and Rechardt *et al.* (2010) calcific tendinitis could be age-related and usually occurs in individuals between the ages of 30 to 40, and is more common in diabetics.

In line with above, there are causes and risk factors of tendinopathy that can act alone or in combination to cause supraspinatus tendon degeneration. According to different authors (Longo *et al.*, 2011; Porcellini *et al.*, 2011), repetitive use of the arms at or above the shoulder level leads to fatigues and damage to the rotator cuff tendons. This can lead to tendon injury with recurrence if the rate of tissue breakdown exceeds the rate of tissue healing, often referred to as Repetitive Strain Injury (RSI). The authors maintain that increase in age leads to decreased capacity for tissue repair and healing with accompanying susceptibility to injury and delayed recovery in the event of injury (Longo *et al.*, 2011; Porcellini *et al.*, 2011).

Many authors agree that the ergonomics associated with the repetitive motion activity is a risk factor (Miranda, Viikari-Juntura, Punnett & Riihimäki, 2008; Binderup, Arendt-Nielsen & Madeleine 2010). The authors collectively agreed that poor posture like slumping of the shoulder forward that causes narrowing of the space for the rotation of the rotator cuff tendons can lead to the abrasion of the tendon as one of the causes of tendinopathy. The authors further stated that

repetitive or solitary injury to the shoulder can lead to stiffness in the bursa or capsulitis especially the posterior capsule. When this occurs, the ball slides upward on the socket when reaching and lifting objects leading to abrasion of the rotator cuff on the acromion bone and coracoacromial ligament that form the roof above the tendons (Miranda, Viikari-Juntura, Punnett & Riihimäki, 2008; Binderup, Arendt-Nielsen & Madeleine 2010). In a similar report by Luo *et al.* (1998), shoulder instability like very lax shoulder joints (wide range of motion) and hypermobility could be associated with rotator cuff impingement on the acromion bone and coracoacromial ligament.

Other factors considered by authors include smoking; this can damage the circulation to tendons and bones thereby placing these tissues at risk for injury, and can slow or prevent their healing during recovery (Kane, Dave, Haque & Langston, 2006; Baumgarten *et al.*, 2010). In sex prevalence, tendinopathy is more common in males. Maffulli, Wong & Almekinders (2003) maintain that Achilles tendon tears occur 4 to 7 times more often in males than females as tendons deteriorate with age. In agreement to this, Steele (2009) says that middle-aged individuals are more probable to develop tendinitis. On the contrary, a study of track and field athletes by Longo *et al.* (2009) showed that gender, weight, height, or impact profile did not influence the development of Achilles tendinopathy.

In summary, the above theories on the aetiology, pathophysiology and risk factors of tendinopathy show that aetiology of supraspinatus tendinopathy is multifactorial. This is because the pathophysiology process is varied and the risk factors are diverse. This understanding is vital in view of the clinical indications of the patients in this study as indicated in the background section of chapter 1. This significance is reflected in a review of the mechanisms of pain and how this relates with tendinopathy experienced in the shoulder

2.2.2 Mechanism of pain and its relation to tendinopathy

Bearing in mind the key focus of this research which was to measure the strain ratio of supraspinatus tendon and measure the accuracy of sonoelastography in the diagnosis of supraspinatus tendinopathy, this review noted that shoulder pain is one of the indications for supraspinatus tendinopathy. According to Roquelaure *et al.* (2006), the actual cause of pain in rotator cuff disease is not properly understood. In the same vein, Mall *et al.* (2010) and Yamamoto *et al.* (2011) agree that the mechanism and the relationship between pain and tendinopathy appears to be unclear. In a study by Moosmayer and colleagues on the MRI of symptomatic and asymptomatic full-thickness rotator cuff tears, they found out that some cuff tears are painless while tendinopathy with or without tears cause excruciating pain (Moosmayer, Tariq, Stiris & Smith, 2010). However, some theories have been put forward by different researchers to elucidate it.

A literature identified was a review paper by Sharma and Maffulli (2005) on "Tendon injury and tendinopathy: healing and repair". It posited an orthodox theory which maintains that inflammation and its mediators like prostaglandins and prostacyclins cause pain. In very chronic forms, the paper says, pain could be due to collagen fibre separation. A more recent theory by Ackermann, Salo & Hart, (2009) however, is of the opinion that biochemical stimulation of nociceptors and other biochemical irritants cause pain. In another vein, there is new information that suggests that non-neuronal cholinergic system plays an important role in the chronically painful tendons and in inflammatory conditions (Forsgren *et al.*, 2009; Kaux, Forthomme, Le Goff, Crielaard & Croisier, 2011). However, there is evidence posited by several authors that local, non-neuronal production of catecholamines in the fibroblasts at the muscle origin of lateral and medial epicondyles in patients suffering from golf and tennis elbow could have an effect on blood vessel regulation and pain mechanisms (Zeisig, Ljung, Alfredson & Danielson 2009; Kaux, Forthomme, Le Goff, Crielaard & Croisier, 2011).

According to Lewis (2009), the absence of good agreement in treatment could result in chronic pain and repeated tendinopathies. Lewis (2009) continued and

stated that while passive treatment is ineffective in conditions that would require active treatment such as new therapies (application of platelet-rich plasma or extracorporeal shock waves), eccentric exercises resulting in what is referred to as 'mechanotransduction' can be quite effective. Mechanotransduction is a process whereby mechanical loading is converted into cellular response by the body and thereby enhancing structural changes (Khan and Scott, 2009; Kaux *et al.*, 2011). This process promotes collagen fibril alignment which results in stronger tensile strength, increased fibroblast activity and collagen formation. Other authors agreed that it prevents adhesion between healing tendons and adjacent tissues (Stasinopoulos, Stasinopoulou & Johnson, 2005; Barone, Bellafiore, Leonardi & Zummo, 2009).

This review identified two studies by Cook *et al.* (2001b) and Khan *et al.* (2003) that demonstrated that signs of 'degeneration' were present in asymptomatic tendons using MRI and ultrasound while some painful tendons appeared normal (Cook *et al.*, 2001b; Khan *et al.*, 2003). In agreement to this, this evidence of degeneration has already been demonstrated in a control group of cadaveric tendons by Kannus & Josza (1991). One, therefore, can surmise that a positive imaging diagnosis could indicate pathology though it might be sub-clinical (Cook *et al.*, 2000). Tendon imaging using sonoelastography could be a useful tool in screening for pathology and could predict tendon injury before it becomes symptomatic. According to Fredberg & Bolvig (2002), this in turn would provide the clinician and athlete/patient time for rehabilitation before the tendon becomes symptomatic. It is in the light of this that this research was undertaken to investigate if and how sonoelastography provides this information. Such information is useful in tendon grading and strain ratio to predict early or subclinical tendinopathy which is the focus of this thesis. This point was followed by an evaluation of the clinical diagnosis in the management of tendinopathy.

2.2.3 Impact of clinical diagnosis in the management of tendinopathy

In an evaluation of the impact of clinical diagnosis in the management of tendinopathy, this literature review explored clinical and functional classification for tendinopathy which was proposed by Blazina *et al.* (1973). This taxonomy by

Blazina and colleagues involves four stages and has been a general classification for tendinopathy that is still used till date. This was followed by a classification system in three stages by Neer & Welsh (1977) for shoulder tendinopathy. A more recent classification by Kaux *et al.* (2011) involving three stages comprises the chronology of tendinopathy symptoms. For the purpose of this research, a careful adaptation of these different classifications resulted in a modified classification for this research as shown in Appendix I. This modified classification is referred to as Modified classification of Kaux *et al.* (2011); this considered mainly the period of the symptoms demonstrated by the patient regardless of the age of patient.

The chronology of symptoms is classified into 3 stages:

Stage 1 - symptoms present for 0 to 6 weeks, the tendinopathy is characterized as “acute”;

Stage 2 – symptoms between 6 to 12 weeks, regarded as “sub-acute”;

Stage 3 - after more than 3 months, it may be considered as “chronic”.

Several authors have posited that the diagnosis of tendinopathy is primarily clinical. According to Fredberg & Stengaard-Pedersen (2008), tendinopathies are clinically characterized by a slow commencement of tendon stiffness, activity-related pain, reduced function, and occasional localized swelling and palpable crepitations. In line with the clinical manifestation, pain is revealed when clinical testing is carried out. Rees *et al.* (2006) maintained while discussing the current concepts in the management of tendon disorders that it is uncertain at present where the pain in tendinopathy arises from, but certainly tendinopathy is only sometimes painful. The authors disclosed that typically three tests reveal pain during clinical examination namely: stretching, isometric contractions and palpation of the pathological area. This opinion was supported by Fredberg & Stengaard-Pedersen (2008).

However, the role of serial diagnostic imaging is limited due to the poor correlation between diagnostic imaging and symptoms, (Khan *et al.*, 2003). Imaging modalities like Ultrasound and MRI have been mentioned previously for imaging tendinopathies due to their inherent advantages. Ultrasound demonstrates the fine internal structure of tendons showing neovascularization,

thickening of the tendon, discontinuity of fibres, focal hypoechoic intratendinous areas (Fredberg & Stengaard-Pedersen, 2008). A two-year prospective study on the value of ultrasound and MRI in the assessment of Achilles tendinopathy by Khan *et al.* (2003) showed that MRI has extreme sensitivity and this means that structural abnormalities seen by imaging could not precisely correlate with clinical symptom. A critical reflection of works from other authors recommended that a cautious clinical correlation with imaging findings is necessary (Cook, Khan, Kiss, Coleman & Griffiths, 2001b; Khan *et al.*, 2003; Fredberg & Stengaard-Pedersen, 2008). For instance, a comparative study by Warden and Bruckner (2003) of ultrasound and MRI showed ultrasound sensitivity and specificity of patellar tendinopathy as 58% and 94% respectively, and MRI sensitivity and specificity as 78% and 86% respectively ($p < 0.001$). A careful reflection of both results shows disparity in sensitivity and specificity on same clinical conditions. In a similar study by De Zordo *et al.*, (2008), the role of clinical diagnosis in tendinopathy was investigated. The study evaluated the role of sonoelastography in Achilles tendon assessment of consecutive patients and healthy volunteers. The study further compared clinical diagnosis to ultrasound by assessing the proximal, middle and distal third of the tendon. The criteria used by ultrasound to define pathology were tendon thickening and/or intratendinous focal areas, and the criteria used by sonoelastography to define tendon pathology was tissue softening. The results of this study showed that in healthy volunteers, normal findings were present in 100% of clinical diagnosis, in 100% of ultrasound images and in 93% of sonoelastography images. However, in patients, alterations were found in 61% of clinical diagnosis, in 59% of ultrasound images and in 68% of sonoelastography images. Sonoelastography showed a sensitivity of 94%, specificity of 99%, and accuracy of 97%, while ultrasound showed a sensitivity of 93%, specificity of 100% and accuracy of 99%. Correlation (R) between sonoelastography and ultrasound was high with a value of 0.89 ($p < 0.001$) (De Zordo *et al.*, 2008).

Another example was also seen in a similar study carried out by De Zordo *et al.* (2009a) on a different tendon, the common extensor tendon origins in healthy volunteers and patients complaining of lateral epicondylitis. Clinical diagnosis was used as standard of reference. The results in healthy volunteers showed a

similar result to what was seen in the Achilles tendon (De Zordo *et al.* (2008) where normal findings were present in 100% of clinical diagnosis, in 100% of ultrasound images and in 93% of sonoelastography images. In patients, alterations were found in 61% of clinical diagnosis, in 59% of ultrasound images and in 68% of sonoelastography images (De Zordo *et al.*, 2009a). Both studies saw the use of clinical examination as the gold standard as a possible weakness of each study. This was acceptable, however, as no other accurate, non-invasive reference standard was available. Correlation of the results with ultrasound, which is considered to be one of the methods of choice for diagnosing tendinopathy, was high.

Imaging demonstrates poor predictive value when the development of symptoms and clinical findings are considered (Khan, Cook, Taunton & Bonar, 2000). A theory proposed by Cook *et al.* (2001a) implies that severe tendinopathies can remain asymptomatic for a long period before the symptoms begin to manifest. Based on this theory, ultrasound investigation of asymptomatic Achilles tendon would help predict a group with a risk of developing symptoms. It was believed the method would reduce the risk of developing chronic tendinopathies or tendon ruptures (Fredberg *et al.*, 2008). However, Klauser & Peetrans (2010) in their submission insisted that due to the limitation of ultrasound's inability to measure tissue softening seen in 'subclinical' tendinopathy, sonoelastography was suggested as an adjunct to conventional ultrasound to improve diagnostic imaging accuracy of tendinopathy. The aim was to see if sonoelastography could allow earlier detection of subclinical alterations, and be used to identify the 'at risk' tendinopathy. The current research aimed to study this gap in literature. Further study, however, was required to confirm if sonoelastography can add predictive information regarding the development of tendinopathy (Klauser & Peetrans, 2010).

2.2.4 Current evidence on the impact of imaging (US, MRI and SE) in the management of tendinopathy

This review also evaluated the significance and roles of different imaging modalities in the diagnosis and management of supraspinatus tendinopathy in

patients with shoulder pain. It identified ultrasound as a proven imaging method for examining soft tissue structures including tendons. It is useful, cheap, dynamic and portable, and still remains the examination of choice for imaging tendons (Martinoli *et al.*, 2002; Harris & Peduto, 2006). Real-time ultrasound imaging of the rotator cuff tendon demonstrates good sensitivity for diagnosis of rotator cuff injury. A meta-analysis study by de Jesus *et al.* (2009) of sixty-five articles that investigated the accuracy of MRI, MR arthrography, and ultrasound in the diagnosis of rotator cuff tears indicated that there is no statistically significant difference between MRI and ultrasound for the diagnosis of partial-thickness tears. However, the study indicated that ultrasound tends to be more sensitive and more specific than MRI (sensitivity: $\chi^2 = 2.057$, $p = 0.15$; specificity: $\chi^2 = 3.347$, $p = 0.067$) (de Jesus *et al.*, 2009). The limitation of this study was that it was not particular about tendinopathy though this may have resulted in the tears that were investigated.

However, in a different study by Warden *et al.* (2007), ultrasound demonstrated better accuracy than MRI in confirming clinically diagnosed patellar tendinopathy (accuracy – 82% vs 70%; sensitivity – 87% vs 57%; specificity – 82% vs 82%; $p < 0.001$) (Warden *et al.*, 2007). Ultrasound has many significant advantages over MRI. It is known that tissue with few mobile protons emits little or no signal, and, therefore, the internal architecture of the tendon is not well demonstrated with MRI while ultrasound demonstrates fine internal structure of tendons with the anatomic border of the tendon more clearly defined than in MRI (Kamel *et al.*, 2004). Koivunen-Niemela & Parkkola (1995) agree that the “standard deviation” and “range of the mean difference” from repeated measurement are less with ultrasound than with MRI. Also, the operator can freely relate with the patient making the examination less formal and any site of reported pain or tenderness can be directly linked with its real-time appearance on the ultrasound image. The operator makes use of the dynamic real-time nature of ultrasound to evaluate tendons throughout their range of motion. It is also possible to make side-to-side comparison during the ultrasound examination. Authors have shown in their studies that the spatial resolution of ultrasound is higher than that of MRI (Erickson, 1991; Kamel *et al.*, 2004), and ultrasound can demonstrate neovascularization in tendinopathy (Fredberg & Stengaard-Pedersen, 2008).

According to Fredberg and Stengaard-Pedersen, (2008), “today, ultrasound is a well-established first-choice modality and is regarded as the examiner’s extended hand in daily practice, which will never be the case for MRI, and MRI has only a limited place in tendinopathy” (Richards, Dheer & McCall, 2001). Lamb and colleagues maintained that due to the low water levels in tendons, MRI does not easily identify tendon pathology and does not readily define its ‘fibrillar’ structure and any alterations that may occur in tendinopathy. According to their report, tendons and ligaments generally appear ‘dark’ in semi-solid structures, and are demonstrated as ‘white’ or ‘grey’ in pathological conditions due to increased water content. This, however, has been improved upon by the introduction of the ‘magic angle imaging’ which reveals more of the intratendinous architecture (Lambe, Coutts, McArthur & Dangerfield, 2006).

This review also noted that although ultrasound has these characteristic qualities over MRI, literature review has shown that some subtle changes in tendon appearance remain poorly defined by grey-scale ultrasound, and therefore would require a more sensitive method to demonstrate these changes (Frey, 2003; Levin *et al.*, 2005) which are attributed to their inability to measure the mechanical characteristics of these tissues as earlier stated. Therefore, early tendinopathic changes are missed by grey-scale ultrasound, and MRI shows less contrast (or axial) resolution than ultrasound (Erickson, 1991; Kamel, Eid & Mansour, 2004). Tendinopathy, paratendinitis and partial tears in the shoulder pose a serious challenge to distinguish clinically.

Grey-scale ultrasound is the best available reference method for the diagnosis of tendinopathy of the supraspinatus tendon. It gives high resolution images for the detection of the disease. Though ultrasound is considered subjective and operator-dependent (Taggart *et al.*, 2006; Smith, Back, Toms & Hing, 2011) it has given comparable results against MRI with good sensitivity, specificity and positive predictive values (de Jesus *et al.*, 2009).

Three reviewed reports (Gibbon *et al.*, 2000; Blankstein *et al.*, 2001; Fornage, 2003) agreed on the ultrasound characteristics of chronic tendinopathy.

According to their results, patients with chronic tendinopathy showed on ultrasound tendon thickening, discontinuity of the fibres, focal hypoechoic intratendinous areas, loss of fascicle organization, intratendinous focal calcification, partial or complete ruptures, poorly defined borders, and bursitis (Gibbon *et al.*, 2000; Blankstein *et al.*, 2001; Fornage, 2003). In addition, the contours of the tendon might appear deformed with a bumpy appearance according to Fornage (1993) and Fredberg and Stengaard-Pedersen (2008). Recently, quantitative ultrasound in the form of sonoelastography has become more prevalent in research settings (Keller *et al.*, 2009; Goertz *et al.*, 2010). However, limited reliable data have been published for these new quantitative ultrasound measures (Collinger *et al.*, 2009). Measuring elasticity of tendons using sonoelastography provides a way forward because it provides images with increased visual resolution and employs quantitative values and colour maps to improve early detection of pathology. This opinion is corroborated by authors who agreed that sonoelastography imaging is showing an increasing number of applications with evidence of improved accuracy in a typical clinical ultrasound setting and promises to make a vital input to the practice of ultrasound (Konofagou, 2004; Gheorghe *et al.*, 2008).

Changes in the elasticity of tissues result from inflammation or tumours and can cause colour alteration in an elastogram (Frey, 2003). The ability to compress tissues easily can be used to estimate tissue softening (Khoury & Cardinal, 2009). Therefore compressibility property can serve as a useful tool to characterize an intratendinous lesion or peritendinous involvement in the supraspinatus tendon (De Zordo *et al.*, 2009a). In tendinopathy, the tendon becomes progressively softer than its normal hard consistency. The soft feature of the tendon is depicted as a medium-to-soft on the colour map and shows as yellow-to-red in the elastogram (as opposed to usual hard structure which shows as predominant blue and patches of green in the elastogram).

In line with the above summations, in the field of musculoskeletal imaging, sonoelastography has shown improved accuracy of grading muscle lesions and distinguishing muscle tears. A study by Fábrega & Fouto (2006) correlated the sonoelastography and MR images of injured muscle. MRI showed hyper

intensive signal lesions in injured muscle in all patients with dimensions 30 x 22 mm, 30 x 25 mm, 80 mm, 100mm and 150mm. The dimensions of these lesions in sonoelastography were 20 x 22mm, 22 x 10mm, 62mm, 67mm and 100mm respectively. In comparison the size of the lesions in MRI was larger because of the additional signal of oedema, while sonoelastography showed the dimensions of the lesion only. This shows that sonoelastography can improve the discrimination of acute injury, using faster and more economical method of diagnosis.

In addition, a further review of published papers indicate that sonoelastography is valuable in the detection of the intratendinous and peritendinous alterations of common extensors and the Achilles tendons, and facilitates differentiation between healthy and symptomatic tendons with good sensitivity and correlation with ultrasound findings (De Zordo *et al.*, 2009a, 2009b; Hayes, 2006; Shiina, 2007). An example was seen in a study on patients with distraction muscular traumas by Monetti & Minafra (2007). The study showed that sonoelastography findings correlated well with MR and allowed visualization of the lesion and with better definition of its dimensions than MRI. Sonoelastography was invaluable in the diagnosis of acute muscle injury and the quantification of the elasticity of the fibres which was not feasible in MRI (Monetti & Minafra, 2007). In line with the above, Minagawa & Kijima (2007) demonstrated that the elasticity of the coracoacromial ligament could influence the onset and symptoms of rotator cuff disease when sonoelastographic imaging was used.

In a different study undertaken by Abdel Razek & Ezzat (2008), sonoelastography was used to evaluate rotator cuff tendon tears in patients with shoulder pain. It compared the accuracy of sonoelastography with ultrasound and MRI using only colour grading assessment. Sonoelastography changed the diagnosis of partial tear into complete tear in two cases (5%) and the sensitivity and negative predictive value increased from 95% to 97% and from 87% to 93% respectively by adding sonoelastography to the grey-scale ultrasound technique. The study also showed that the differences in tendon stiffness between the healthy volunteers and the patients were statistically significant ($p < 0.0001$). The sonoelastography and MRI findings also showed good correlation ($p < 0.001$).

The study concluded that sonoelastography was a sensitive method in the diagnosis of rotator cuff tears and tendinosis. However, the study did not assess any direct quantification of the tendons using strain ratio. This opinion was corroborated by another author, Trombetti (2008), who reported that sonoelastography applications have the potential to provide wide-reaching benefits and have emerged as a way to characterize the mechanical properties of tissue. A study by Schreiber *et al.* (2009) showed that sonoelastography and MRI are comparable in the detection of supraspinatus tendon fatty atrophy and further revealed that there is loss of normal elastic properties in tendons with atrophy.

A real-time freehand sonoelastography was used to assess the reproducibility and pattern description of the normal Achilles tendon (Drakonaki, Allen & Wilson, 2009). The study showed that the intra- and inter-CC values of the strain index were lower for the transverse plane than for the longitudinal plane (0.43, 0.45, 0.41 and 0.78, 0.66, 0.51, respectively). The study concluded that sonoelastography was feasible and that reproducibility of the strain index was good and higher for longitudinal than transverse elastograms.

The clinical reproducibility of sonoelastography of supraspinatus tendon strain ratio is important for the clinical applicability of this method. At the time of this study, no available published material existed on reproducibility of sonoelastography on supraspinatus tendinopathy. Two studies by Drakonaki, Allen & Wilson (2009) and Jansen *et al.* (2007) have already shown that strain ratio was reproducible in the Achilles tendon with good inter-observer variability of 0.84 in each study. A phantom study by Havre *et al.* (2008) showed a lower value of 0.55-0.56 but the highest value of 0.98 was seen in the breast study by Fraquelli *et al.* (2007b). Similar studies have shown reproducibility in breast sonoelastography (Sporeal *et al.*, 2011; Fraquelli *et al.*, 2007b; Boursier *et al.*, 2008). However, reproducibility was reported to be influenced by the operator's experience (Sporeal *et al.*, 2011). Whether this may have been the reason for a lower value of 0.25 in the study by Yoon *et al.* (2011) remains to be seen as their study showed significant inter-observer variability. The current study aimed to research into this gap in literature.

2.2.5 Review of research and clinical application of sonoelastography of musculoskeletal system

This review also noted that sonoelastography has been successfully used in the assessment of various tendons and muscles. It is been found useful in clinical and therapeutic follow-up of muscular lesions. This opinion was formed in review of the various studies undertaken by Fábrega & Fouto (2006). They indicated that it was possible to assess the elasticity degree of fibres once scar-formation was completed. This was seen to complement ultrasound findings considering the difficulty in diagnosing the real healing of impaired tissues during recovery. This allowed more accurate evaluation of the functional recovery in relation to the actual condition of muscular fibres involved in the repair process (Monetti & Minafra, 2007).

In another study of five patients with distraction muscular traumas, sonoelastography findings were found to correlate well with magnetic resonance image (MRI) and allowed visualization of the lesions and their dimensions (Fábrega & Fouto, 2006). While MRI demonstrated hyper intensive signals of lesions in injured muscle in all patients, sonoelastography showed soft lesions with a harder rim with distortion of the fibres. The study concluded that elastography is a promising method for diagnosis of acute muscle injury and the quantification of the elasticity of the fibres (Fábrega & Fouto, 2006). Sonoelastography has been used to detect the distribution of local muscle stiffness within and between resting and contracting muscles at different muscle lengths. This has the potential to assist clinicians in characterizing muscle injuries and neuromuscular disorders (Shinohara *et al.*, 2010).

While demonstrating that the elasticity of the coracoacromial ligament may influence the onset and symptoms of rotator cuff disease (Minagawa & Kijima, 2007), sonoelastography can improve the discrimination of acute injury, is faster, more accessible, and a more economical method of diagnosis. It shows changes (increased stiffness) in symptomatic tendons (Hayes, 2006) of the Achilles, and

extensors of the elbow, and can be an effective tool for follow-up studies (Shiina, 2007).

Sonoelastography showed excellent correlation with MRI and grey-scale ultrasound. In the 20 healthy volunteers studied by Abel Razek & Ezzat (2008), sonoelastography showed blue colour throughout the tendon, which is consistent with stiff normal tendon tissue and normal findings at grey-scale ultrasound. In the patients with partial tears, sonoelastography showed intratendinous colour alterations (green, yellow, and red) not reaching the bursal or articular aspects. Patients with full tears showed colour alterations reaching the bursal or articular surfaces. The differences in tendon stiffness between the healthy volunteers and the patients (40 patients with shoulder pains) were statistically significant ($p < 0.0001$). The elastography and MRI findings also showed good correlation ($p < 0.001$) (Abdel Razek & Ezzat, 2008).

In addition, sonoelastography was able to diagnose tendinitis and mild synovial effusion in four cases (10%) that had false-negative findings on MRI. Sonoelastography changed the diagnosis of partial tear into complete tear in two cases (5%). The sensitivity and negative predictive value increased from 95% to 97% and from 87% to 93% by adding sonoelastography to the grey-scale ultrasound technique. Sonoelastography was suggested to be used as an easy reproducible follow-up method to monitor treatment (Abdel Razek & Ezzat, 2008). This is an area that requires further study.

Sonoelastography has the potential to determine the timing for the athlete to resume training by assessing the elasticity degree of tissues in recovery (Fredberg & Bolvig, 2002). Sonoelastography has recently started emerging in the study of musculoskeletal conditions involving the Achilles tendon, and tendons in the medial and lateral epicondyles of the elbow. De Zordo *et al.*, (2009a, 2009b) found excellent correlation between grey-scale ultrasound and sonoelastography in their studies on lateral epicondylitis and Achilles tendon. Sonoelastography proved invaluable in the detection of the intratendinous and peritendinous alterations of lateral epicondylitis and facilitated differentiation between healthy and symptomatic extensor tendon origins with excellent

sensitivity and excellent correlation with ultrasound findings (De Zordo *et al.*, 2009a).

The study (De Zordo *et al.*, 2009a) compared sonoelastography findings to clinical examination, and ultrasound findings. Correlation to Power Doppler Ultrasound (PDUS) and pain score, using a visual analogue scale (VAS), was performed. Clinical examination was used as standard of reference. In healthy volunteers, sonoelastographic images showed hard tendon structures in 96% of tendon thirds and mild alterations in 4%. Sonoelastography of patients showed hard structures in 33% of tendon thirds but softening of different grades in 67%, a statistically significant difference in relation to the findings in healthy volunteers ($p < 0.001$). Using sonoelastography a sensitivity of 100%, a specificity of 89%, an accuracy of 94%, a positive predictive value of 88% and a negative predictive value of 100% were found, whereas ultrasound showed a sensitivity of 95%, a specificity of 89%, an accuracy of 91%, a positive predictive value of 88% and a negative predictive value of 95%. Sonoelastography showed excellent correlation to ultrasound findings ($R > 0.900$). No correlation between ultrasound and PDUS or sonoelastography and PDUS was detected, but PDUS showed a strong correlation with VAS score.

This review also evaluated the impact of research on a biomechanical study of muscles by Pel, Spoor, Goossens, & Pool-Goudzwaard (2008). An evaluation of a subjective report of shoulder bursitis in polymyalgia rheumatic by Cantini *et al.*, (2001) was also undertaken. Both studies demonstrated colour change as the method of distinguishing tissue changes. Colour change, however, does not have the capacity to demonstrate quantitative tissue measurement. The current study aimed to assess this through strain ratio measurement.

2.2.6 Outcome measures of sonoelastography and its influence in demonstrating a change in practice for improved patient management

The dearth of literature on sonoelastography of MSK system and follow-up studies was a limitation of this study. In this literature review, evaluation of other anatomic structures such as the thyroid, testes, breast, pancreas, salivary gland

and lymph nodes was necessary to reflect comparative assessment with MSK system and the importance of correlation and follow-up studies using sonoelastography. It was necessary to include these anatomic structures for comparative assessment of quantitative measures as currently there are no published data on supraspinatus tendon strain ratio and ROC curves with area under curve (AUC) assessment. In view of these, this literature review included relevant information from these anatomic structures in order to elucidate the potential of sonoelastography in improving specificity of ultrasound. This also underlines the objective of this research to achieve a comprehensive and critical literature review.

In an evaluation of the impact of sonoelastography and its influence on how to demonstrate a change in practice for the diagnosis and management of supraspinatus tendinopathy in patients with shoulder pain, this review noted that the technique of sonoelastography is fast gaining ground in the field of diagnostic imaging as it now used as a useful adjunct tool for ultrasound diagnosis (Garra, 2011). There are no clear-cut opinions against it as many manufacturers of ultrasound machines are rapidly incorporating sonoelastography into their software with a view to improving the diagnostic capacity of their equipment.

In a review paper (Garra, 2007), the author maintained that with four commercial ultrasound scanners already offering elastography and more to follow, this technique was likely to be the most widely used for the near future. The advantage is that elasticity imaging is achievable for virtually every tissue. It is well known that breast elastography has potential for improving the specificity of ultrasound and mammography for cancer diagnosis (Barr 2010; Leong *et al.*, 2010; Raza *et al.*, 2010). Elastography has also successfully imaged lesions in the thyroid, prostate gland, pancreas, and lymph nodes. Elastography has shown great potential in the evaluation of diffuse disease including cirrhosis and transplant rejection while vascular imaging of the myocardium, blood vessel wall, plaque, and venous thrombi has also shown great potential. It is proposed that sonoelastography imaging could be useful in assessing the progress of ablation therapy and monitoring the severity of lymphoedema (Garra, 2007).

In a recent study by Ishikawa *et al.* (2011), sonoelastography showed that colonoscopic findings correlated with disease activity among 37 patients with ulcerative colitis where 10 cases were classified as normal, 11 as homogeneous, 6 as random, and 10 as hard. Sonoelastography findings revealed a significant correlation with colonoscopy ($p < 0.001$). Endoscopic sonoelastography is a rapidly advancing field and it has been employed in the investigation of lymph nodes and the pancreas. The accuracy of sonoelastography was reported to be 85% to 90% for the differentiation of benign and malignant lymph nodes (Janssen, 2008). This proves sonoelastography to be useful in selecting lymph nodes appropriate for biopsy. The sonoelastography pattern for malignant tumour of the pancreas appeared different from that of normal pancreas according to the study. However, this malignant pattern was similar to that of chronic pancreatitis as they seem to have the same biomechanical architecture. The study suggested that it was possible that early diagnosis of cancer in a patient with chronic pancreatitis would not be enhanced by sonoelastography. Irrespective of this limitation, endoscopic sonoelastography is a promising method, and prospective studies will be needed to define appropriate applications of its clinical significance (Janssen, 2008). The importance of sonoelastography in follow-up studies is gaining ground. In a study by Aigner *et al.* (2012) involving 50 testicular lesions, 34 (68%) were tumourous and 16 (32%) were non-tumourous in origin. Sonoelastography showed hard lesions appearance in all cases of testicular tumours and three cases of non-tumourous lesions. Four lesions with an unsure diagnosis on ultrasound and colour and/or power Doppler ultrasound were soft at sonoelastography and showed non-tumourous appearance at follow-up. Sonoelastography showed a sensitivity of 100%, a specificity of 81%, a negative predictive value of 100%, a positive predictive value of 92%, and an accuracy of 94% in the diagnosis of testicular tumours. This report shows that sonoelastography can provide additional information in cases with equivocal ultrasound findings because of its high specificity (Aigner *et al.*, 2012).

One major limitation of fine needle aspiration biopsy (FNAB) technique is its invasiveness though it is the gold standard for diagnosis of lymphoma in Hashimoto's thyroiditis. Sonoelastography is non-invasive, and its accuracy in

differentiating between true and pseudonodules was compared with ultrasound in the study by Yildirim *et al.* (2011) using FNAB as gold standard in 54 patients with Hashimoto's thyroiditis. Sonoelastography findings were in agreement with the cytopathological results and demonstrated that sonoelastography was able to detect true thyroid nodules often misdiagnosed by US. Yildirim *et al.* (2011) surmised that sonoelastography demonstrated increased sensitivity for true nodule diagnosis when compared with ultrasound and could eliminate unnecessary FNABs being carried out.

Two different studies investigated major salivary gland tumours using sonoelastography and revealed that it is a limited technique in the differential diagnosis between benign and malignant salivary masses (Bhatia *et al.*, 2010; Dumitriu *et al.*, 2011). Dumitriu *et al.* (2011) found out in their study that the difference in elastographic score between benign and malignant tumours overall was statistically significant ($p < 0.05$), but the difference between malignant tumours and pleomorphic adenomas and that between Warthin tumours and pleomorphic adenomas were not statistically significant. They used cut-off values between scores 2 and 3 and scores 3 and 4, and found no statistically significant difference between benign and malignant tumours. Bhatia and colleagues (2010) concluded in their study that qualitative sonoelastography was likely to have a poor ability to discriminate benign lesions particularly pleomorphic adenomas from malignant disease (Bhatia *et al.*, 2010). In a study by Ueno (2010) that compared sonoelastography and ultrasound with histological correlation on the decision to biopsy in breast lesions, the authors found out that the mean elasticity score of malignant lesions was higher than that of benign lesions. In order to make a decision whether to biopsy, ultrasound showed higher sensitivity than sonoelastography (98.5% vs. 93.2%), ($p < 0.001$), while sonoelastography demonstrated higher specificity than ultrasound (42.6% vs. 16.3%) ($p < 0.001$). The authors concluded that due to the higher specificity of sonoelastography in distinguishing benign from malignant lesions, it showed the potential to reduce biopsies with benign results since lesion stiffness on sonoelastography was well correlated with the malignant potential of the lesion.

Quantitative sonoelastography was compared to conventional qualitative sonoelastography and ultrasound in a study by Xing *et al.* (2011) for thyroid nodule characterization based on the premise that initial data suggested sonoelastography can improve the specificity of ultrasound for differentiating benign and malignant thyroid lesions. The authors used the strain ratios of thyroid tissue to the nodule to assess quantitative characterization. ROC curve analysis was adopted to compare the diagnostic performance of the strain ratio and that of ultrasound. Histological findings were used as the reference point. With a ROC cut-off of 3.79, significantly different strain ratios for benign (mean $\hat{A} \pm SD$, $2.97 \hat{A} \pm 4.35$) and malignant ($11.59 \hat{A} \pm 10.32$) lesions was obtained ($p < 0.0001$). The strain ratio measurement had 97.8% sensitivity and 85.7% specificity. The area under the curve for the strain ratio was 0.92, whereas that for the 4-point scoring system was 0.85. Of the ultrasound patterns, microcalcification had the highest area under the curve, at 0.72. The authors concluded that strain ratio measurement of thyroid lesions is a quick standardized method for analyzing stiffness within examined areas, and could be an add-on to conventional ultrasound to increase the diagnostic performance of the examination (Xing *et al.*, 2011).

A similar study by Cakir *et al.* (2011) used strain index (SI) and sonoelastography to score thyroid nodules and establish the role for these parameters in the differential diagnosis of thyroid nodules. The study used histopathological analysis as reference standard and their results were comparable to those of Xing *et al.* (2011). The study indicated that measurement of SI with sonoelastography as a non-invasive procedure could be used as an adjunctive method to the grey-scale ultrasound for the differential diagnosis of thyroid nodules (Cakir *et al.*, 2011). Recent advances in sonoelastography consist of quantification using strain ratios, acoustic radiation force impulse imaging, and shear wave velocity estimation. These are valuable for characterizing focal masses and also for diagnosing diffuse organ diseases such as cirrhotic liver disease (Garra, 2011). Other promising applications of sonoelastography include atheromatous plaque and arterial wall evaluation, venous thrombus evaluation, graft rejection, and monitoring of tumour ablation therapy. Garra (2011) maintained that when considering the purchase of a

system with sonoelastography in this rapidly developing field, it would be important to be sure the manufacturer's plans for future upgrades included quantification.

MRI has high sensitivity for rotator cuff tears especially the supraspinatus tendon. However, there is less use of MRI to diagnose tendinopathy due to high cost, limited availability and greater use of musculoskeletal (MSK) ultrasound. MSK ultrasound offers many advantages which include lower cost, better availability/portability, better patient tolerance, real-time capability, higher spatial resolution, guided intervention, first line imaging e.g. for rotator cuff tears/tendinopathy, excellent dynamic capability, examining multiple planes, and improved evaluation of extremities.

The current issues and challenges surrounding sonoelastography include the fact that MRI and histology remain the gold standard in some aspects of MSK ultrasound, while sonoelastography is an important tool that does not increase scanning time and has the potential to improve diagnostic accuracy. Sonoelastography could be an important and useful addition to triage that will reduce cost and patient waiting time. The freehand technique is reproducible and remains the popular choice, though it is questioned in some circles (Drakonaki, Allen & Wilson, 2009). About 90% of published materials on SE used freehand technique. According to Drakonaki and colleagues, reproducibility is influenced by the operator's experience, and intra- and inter-observer variability is seen to show good results though Nazarian (2007) considered it a limitation. There is need to recognize the limitations of MSK ultrasound and make appropriate referrals. When further intervention is indicated, sonoelastography can offer more accurate location for precise targeting of a lesion. Strain ratio data from sonoelastography can ensure quantitative measurements are available from the strain ratio tool. Sonoelastography has been shown to increase the specificity of grey-scale ultrasound, adding new benign criteria and thereby eliminating unnecessary diagnostic procedures.

2.2.7 Synopsis of current evidence on sonoelastography

On the strength of available evidence, sonoelastography imaging of other organs such as the breast, internal organs, reproductive and superficial organs revealed increased sensitivity and specificity, and accurate prediction of malignancy in most conditions (Cochlin, Ganatra & Griffiths, 2002; Lyshchik *et al.*, 2005; Miyanaga *et al.*, 2006; Rago *et al.*, 2007; Tsutsumi *et al.*, 2007). Especially in the breast and thyroid, researchers have praised the potential of the technique to considerably reduce benign breast biopsy rates, and play a more modest, supporting role to mammography and conventional ultrasound.

However, recent studies by Mori *et al.*, (2012) and Farrokh, Wojcininski & Degenhardt (2013) have shown that false negatives do occur in elasticity evaluation though it is simple to perform. Typical false negative lesions were seen as “soft” lesions in mucinous carcinoma, cystic carcinoma or inflammatory cancer (Mori *et al.*, 2012). In their study (Farrokh, Wojcininski & Degenhardt, 2013), sonoelastography showed a false negative of 25% in mucinous carcinoma and the technique performed significantly worse in lesions > 20 mm in diameter (sensitivity = 61.1%, specificity = 97.2%) than in lesions < 20 mm in diameter (sensitivity = 92.6%, specificity = 96.2%). This finding was attributed to tumour depth. These recent advances have shown the potential of sonoelastography in view of its limitations in clinical settings which hopes to make a constructive input to the practice of ultrasound (Konofagou, 2004).

The choice of ultrasound or MRI has traditionally been determined by the clinician based on personal preference and experience rather than on evidence-based guidelines. A number of studies evaluated the accuracy and sensitivity of ultrasound (0.63–0.83 and 0.68–0.87, respectively) (Kainberger *et al.*, 1990; Warden *et al.*, 2007; Khan *et al.*, 1997; Nehrer *et al.*, 1997; Khan *et al.*, 2003), and MRI (0.68–0.70 and 0.50–0.57, respectively) (Warden *et al.*, 2007; Khan *et al.*, 2003; Adams, Schoolfield & Burkhart, 2010) in detecting tendinopathy in different tendons. Direct comparison between the two modalities showed ultrasound, in trained hands, to be more accurate than MRI due to the superior spatial resolution of ultrasound imaging (Warden *et al.*, 2007; 1997; Khan *et al.*,

2003; Rasmussen, 2000; Filippucci *et al.*, 2007). These studies used clinical diagnosis as the yardstick in determining the accuracy and sensitivity.

However, the phenomenon that imaging abnormalities do not necessarily signal the presence of clinically significant symptoms has been well established. Cook *et al.* (1998) reported that 22% of elite athletes demonstrated pathological lesions within the patellar tendon, despite the absence of anterior knee pain. Importantly, the presence of asymptomatic structural abnormalities within tendons identified using imaging has been shown to increase the risk of developing pain (Malliaras *et al.*, 2006; Comin *et al.*, 2013). With regard to the rotator cuff, early studies indicated a progressive course of rotator cuff tendinopathy (Yamanaka & Matsumoto, 1994; Kartus *et al.*, 2006). However, a recent study reported a low risk for tear progression in small, symptomatic supraspinatus tears (25% in 3.5 years) (Fucentese *et al.*, 2012). The progression of rotator cuff tendinopathy is associated with increased symptom manifestation (Yamaguchi *et al.*, 2001; Mall *et al.*, 2010). Investigators are developing more reliable and sensitive methods of quantitative tendon imaging, but these methods are, at this point in time, more relevant for research than for clinical practice (Scott *et al.*, 2012).

The main purpose of this study was to investigate the accuracy of sonoelastography in the assessment of supraspinatus tendinopathy in patients with shoulder pain. One important observation is that some researchers have provided some quantification methods of strain and deformability calculations known as strain values in the breast and thyroids. This is unlike in the musculoskeletal system where a few quantification methods have been described for the Achilles tendon (Drakonaki, Allen & Wilson, 2009; Palle *et al.*, 2011). There is no published data on quantification of the supraspinatus tendinopathy which informed the need for this study.

On these evidences, elasticity imaging showed an increasing number of applications with evidence of improved accuracy in a typical, clinical ultrasound setting (Konofagou, 2004; Gheorghe *et al.*, 2008). This justified the need for further studies to investigate the elasticity of the supraspinatus tendon in normal

subjects and painful shoulders. A study using real time freehand ultrasound elastography to assess the reproducibility and pattern description of the normal Achilles tendon (Drakonaki, Allen & Wilson, 2009) showed that the method was feasible and that the reproducibility of the strain index was good and higher for longitudinal elastograms. They recommended that further studies were needed to assess the clinical value of the method.

There are a limited number of studies on the supraspinatus tendon (Budgie, 2008; Abdel Razek & Ezzat, 2008) and there has been no published extensive study on the accuracy of SE in assessing supraspinatus tendinopathy in patients with shoulder pain. These justified the need for further studies to investigate the role of sonoelastography in the early detection of supraspinatus tendinopathy in patients with shoulder pain.

2.2.8 The effect of side dominance in this research.

As stated in the background of this thesis in Chapter one, a review of literature on sonoelastography indicated that the effect of side dominance has not been fully investigated in current literature on the subject. However, in a recent study of ultrasound dimensions of the rotator cuff in young healthy adults by Karthikeyan and colleagues (2014), the authors demonstrated the mean maximum width of the supraspinatus footprint in the patients examined. The footprint for the dominant arm measured 13.4 mm, and 13.5 mm for the nondominant arm in women ($p < 0.001$; *t-test*). In men, the footprint for the dominant arm measured 14.9 mm, and 14.9 mm for the nondominant arm ($p < 0.001$; *t-test*). The mean difference in supraspinatus footprint dimensions between the dominant and nondominant arms was 0.03 mm in men ($p = 0.867$; paired *t-test*) and 0.09 mm ($p = 0.607$; paired *t-test*) in women (Karthikeyan *et al.*, 2014).

However, the thickness of the supraspinatus tendon at the footprint was significantly different between the dominant and nondominant arms in men and women. The difference in thickness was 0.5 mm ($p = 0.003$; paired *t-test*) in men

and 0.3 mm ($p = 0.005$; paired *t-test*) in women at the medial edge of the footprint; at the middle of the footprint it was 0.3 mm ($p = 0.022$; paired *t-test*) in men and 0.27 mm ($p = 0.007$; paired *t-test*) in women (Karthikeyan *et al.*, 2014).

The importance of this finding, according to the authors, is that asymptomatic contralateral shoulders can be used as a guide to estimate normal dimensions of the affected shoulder. This appears to concur with the methodology of the current research that did not consider the effect of side dominance. Therefore it remains to be seen if there will be any significant effect of side dominance when investigated with sonoelastography since sonoelastography measures tendon elasticity and not size. There is a probability that increased thickness may affect compressibility of the supraspinatus tendon though the degree of compression applied in sonoelastography is so remarkably small. This will be an area of future study.

2.2.9 Limitations of sonoelastographic tendon imaging

This literature review also noted that in-line with the fact that no imaging technique is perfect and without its own challenges. The use of sonoelastography in practice has not been an exception as indicated in the submissions indicated below. It was discovered that a major limitation of real-time sonoelastography is operator dependency as pressure is applied with the use of a free-hand technique. It is argued that this might affect reproducibility. The question regarding the appropriate level of pressure to be applied using freehand technique has been dealt with. Ito *et al.* (2006) defined it as a level of pressure that maintains contact with the skin and permits imaging conditions for which the association between pressure and strain is essentially proportional. Moderating the pressure exerted with the ultrasound probe to avoid overly high and very low pressures is important because of the nonlinear properties of tissue elasticity (Itoh *et al.*, 2006; Klauser, Faschingbauer & Jaschke, 2010; Srinivasan & Dubey, 2012).

Near-proportional relationship between pressure exerted and tissue strain should be maintained. This can be monitored using the visual indicator scale on the

machine which gives an optimal dynamic range of pressure, because when the pressure decreases or increases below a certain level, the pattern of the elasticity image starts to change drastically. Monitoring the visual indicator helps to decrease inter-observer variability and ease image acquisition. Image acquisition is best in the compression phase when best contrast images are available (Itoh *et al.*, 2006). A visual indicator between 3 and 4 on the Hitachi ultrasound machine is considered to give optimum compression for image acquisition.

This review also noted that a minimum number of two to three compression and decompression cycles should be performed for every supraspinatus tendon. In patellar tendons at least three cycles are performed for every third and images saved from each cycle (Klauser, Faschingbauer & Jaschke, 2010). It is believed that sonoelastography at the start and finish of each pressure cycle fails to provide correct elastograms due to incorrect calculation of elasticity of initial and late scans. However, the results are not affected by this artefact when the required images are obtained during compression. Multicompression imaging is used to improve the signal-to-noise ratio of sonoelastography images (Konofagou, Ophir, Kallel & Varghese, 1997; Skovoroda, Emelianov & O'Donnell, 1995)

In addition, elasticity changes constantly at the border of the transducer in longitudinal scans. This can be as a result of inhomogeneous pressure application. This effect can lead to tissue shifting due to unilateral compression which might influence elastograms at the border. This is another potential limitation. Division of the Achilles tendon in three thirds allows for overlapping scans so that results of the borders of longitudinal scans are not included in the diagnostic process. In the supraspinatus tendon, the tendon is not divided into sections. This could explain why longitudinal sections were used for the present study as tissue shifting would be more pronounced if transverse sections were used. In the patellar tendon, the use of a gel standoff pad can help to alleviate this problem. However, the magnitude of the compression is argued to not overtly cause any significant shift.

The dimension of the sonoelastography window or ROI influences elastograms as a mean of elasticity of each image pair is calculated by sonoelastography. A larger ROI that includes more neighbouring soft tissue makes a tendon present harder appearance with more blue colour than a smaller ROI where less soft adjacent tissue is added. It is recommended that the ROI or box is standardized. In a study on Achilles tendon, the authors recommended that the depth of the ROI should be three times the tendon size and width, and about three quarters of the screen for longitudinal scans (Klauser, Faschingbauer & Jaschke, 2010). Nonetheless, sonoelastography in its current status is a strongly subjective technique. Both training and interpretive skills are required.

An additional technical limitation of sonoelastography displayed in Achilles tendons is that elastograms are calculated only at a distance of ≥ 1.2 mm from the probe. In slim individuals, skin-to-tendon distance is often < 1.2 mm, and therefore correct elastograms cannot be obtained without using a gel pad in the Achilles tendon which appears to be the best way to resolve this limitation (Klauser, Faschingbauer & Jaschke, 2010). However in supraspinatus tendon, the presence of the deltoid muscle compensates and reduces the effect of this limitation but does not completely eliminate it.

There are no precise agreements on the issue of inter-observer and intra-observer variability in sonoelastography imaging of tendons. Literature evidence varies and due to the operator dependency of the technique it is yet to be certain how much impact this has (Nazarian, 2007). There are yet no adequate quantitative measurements to perfectly characterize the mixture of tissue hardness depicted by elastography images. The qualitative pattern analysis of the elastography images is clearly subject to errors due to inter-observer and intra-observer variability (Gheorghe, Iacob & Gheorghe, 2008). Image construction in sonoelastography leads to certain soft-tissue artefacts as demonstrated in the study on Achilles tendon and common extensor tendon as well as in surrounding bony structures according to De Zordo *et al.* (2009a; 2009b). However, with further practice, it was possible to differentiate the artefacts from consistent images. Also, repeating the scan three times helped to reduce this limitation.

The supraspinatus tendon is put under tension by fully abducting it from its original physiological position when scanned. As a result, it was argued that the outcome of the sonoelastography of the supraspinatus tendon was unreliable at the periphery of the image where probe compression force was markedly reduced due to curvilinear path of the tendon as this was a challenging technique. However, there was a varying opinion that this position is not reliably reproduced in different subjects (Sconfienza *et al.*, 2012). It is important to note that most literature evidence of pitfalls and limitations in imaging the tendon were based on early stages of observations and there are currently few existing published materials on the supraspinatus tendon.

Like most applications, real-time sonoelastographic imaging limitations can be overcome by better quantification tool (e.g. strain ratio, histogram analysis, use of lower examination frequencies (current study used 13-16 MHz; initial studies used 8-10 MHz), and use of broadband transducers (Ciurea *et al.*, 2011). From technological point of view, generating identical and consistent field of vibration all through the region of interest and surmounting the gap between greyscale ultrasound resolution against tissue hardness estimation still remain limitations.

Sonoelastography provides additional information that would help broaden its use in musculoskeletal imaging. This, however, would depend on enhancing the capability to interpret sonoelastographic artefacts and take advantage of the information it provides (Klauser, Faschingbauer & Jaschke, 2010).

2.2.10 Conclusion

This chapter has reviewed current concepts on the aetiology of supraspinatus tendinopathy with emphasis on pathophysiologic conditions which influence this condition. It has reviewed the nature and factors which influence disorders of rotator cuff tendons which are often chronic and can be difficult to manage successfully. A critique of the mechanism of pain and its relationship to tendinopathy has also been discussed. All these were done by examining the relationship between clinical diagnosis and imaging of tendinopathy as it relates

with sonoelastography. Different outcomes and measures of sonoelastography which have the capacity to influence and demonstrate opportunities for change in practice which could lead to improvement in patient management have also been discussed in this chapter. A careful evaluation of current evidence on the current evidence on the use of sonoelastography in other areas of medical imaging as well as a reflection on the likely effect of side dominance on shoulder imaging has also been undertaken. Attempts have also been made to review current evidence on the impact of different imaging modalities in the management of tendinopathy. The chapter concludes with a reflection on the limitations of sonoelastographic tendon imaging in an attempt to identify areas and gaps in current knowledge which prompted the need for this research.

The next chapter presents the first phase of this study in which normal and healthy volunteers who were asymptomatic were examined.

Chapter 3 – Phase 1 Study

Establishing normal parameters for diagnostic tests of supraspinatus tendons in healthy volunteers –“asymptomatic” group

3.1 Introduction

This chapter starts with a preview of the criteria for the diagnostic test used in this research. Then it presents the first phase of this study where asymptomatic healthy volunteers were examined. This first phase investigated healthy volunteers to establish normal parameters for the diagnosis of supraspinatus tendinopathy. The elasticity of supraspinatus tendon was measured. The findings were used to develop strain ratio values for the tendons. These results were used to establish baseline data for the next stage of the research involving patients with shoulder pain. This study served as a control group and ensured an unbiased comparison between sonoelastography (the index test) and grey-scale ultrasound (the reference test) (Bossuyt *et al.*, 2003).

A diagnostic research design was used for this study. This was done after considering and reviewing available literature evidence on previous studies (Moons, Biesheuvel & Grobbee, 2004; Hunink & Krestin, 2002). Diagnostic research was also considered suitable because the focus of this study is similar to other studies where the objective was to quantify the contributions of an additional test beyond test results readily available (Bossuyt *et al.*, 2003). In this case, it was to assess the contributions of sonoelastography using strain ratio values to already existing methods of diagnosing supraspinatus tendinopathy that use grey scale ultrasound and clinical diagnosis.

Preview of the criteria for the diagnostic test used in this research: Phase III diagnostic Test

There is need for rigorous evaluation of diagnostic tests before they are introduced into clinical practice in order to reduce the number of unwanted and misleading estimates of test accuracy (Bossuyt *et al.*, 2003). Bradely (2005) maintains that a new diagnostic test must be thoroughly researched and rigorously tested before it can be introduced into a clinical setting. This is to ensure both validity and reliability. In order to estimate the ability of a new test a

four phase study is required (Sackett & Haynes, 2002a). There are existing several ways of studying the diagnostic value of a new test. Each way is suitable to a type of question and inappropriate to another. In other words, diagnostic studies should match methods to diagnostic questions (Sackett & Haynes, 2002a). This is clearly demonstrated in this research. Among the probable questions, three are the most appropriate as used in this research and demonstrated below.

Phase I question – *Do test results in patients with the target disorder differ from those in normal people?* Put in the context of this research, can sonoelastography distinguish between patients with tendinopathy from normal participants who do not have tendinopathy?

Phase I study was typically conducted among a group of patients known to have the disease and a group of people definitely known not to have it.

Phase II question – *Are patients with certain test results more likely to have the target disorder than patients with other test results?* Put in the context of this research, when sonoelastography is used with clinical diagnosis, are patients more likely to have positive result for tendinopathy than with ultrasound?

Phase II study typically measured sonoelastography colour grades and strain ratio values in normal controls and patients clinically diagnosed with tendinopathy; colour grades 2 and 3, and strain ratio values below cut-off 4.0 were used to distinguish patients with tendinopathy from normal controls.

Phase III question – *Do the test result distinguish patients with and without the target disorder among patients in whom it is clinically reasonable to suspect that the disease is present?* Put in the context of this research, among patients in whom it is clinically sensible to suspect tendinopathy, does the colour grades (yellow and red) and strain ratio value of <4.0 distinguish patients with and without tendinopathy?

The aim of the Phase III diagnostic test is to estimate the diagnostic accuracy of the test under evaluation, called the index test (Bossuyt *et al.*, 2003). Diagnostic

accuracy simply refers to the degree of agreement between the index test and the reference (gold) standard. A gold or reference standard, according to Guyatt & Rennie (2002), is a method having established or widely accepted accuracy for determining a diagnosis, providing a standard to which a new screening or diagnostic test can be carried out.

This phase determines if sonoelastography and strain values are really useful in patients clinically suspected of having tendinopathy. In this Phase III, patients with suspected tendinopathy (n = 204) underwent independent ultrasound, sonoelastography and strain ratio measurements.

The test characteristics include:

CI: confidence interval (95%)

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Likelihood ratio for an abnormal test result

Likelihood ratio for a normal test result

In order to objectively evaluate the accuracy of a diagnostic test, the results of the diagnostic test (index test) is compared with the results of the reference test (gold standard) carried out on the same subject. This is assessed by the number of the participants classified as disease-free or diseased. The validation of this study is usually expressed in a 2x2 table. A typical structure of the table is shown in Appendix J.

In summary, this research is an example of a Phase III study that tested the diagnostic accuracy of sonoelastography using strain ratio against grey-scale ultrasound in assessing supraspinatus tendinopathy in painful shoulders.

3.2 Methodology

A sample group of 284 shoulders of adult normal volunteers were examined. This group is referred to as “the asymptomatic group” and was investigated using grey-scale ultrasound and sonoelastography to establish baseline measurements. The results of this stage presented sonograms and sonoelastograms with strain ratio values of normal supraspinatus. The results

addressed the second objective of the study which was to establish baseline measurements (in the form of strain ratio).

The format of reporting this study is line with the recommended STARD format which includes: introduction, method, result and discussion. This format introduces accuracy, clarity and completeness of the information used in the reporting of studies (Bossuyt *et al.*, 2003; Standards for the Reporting of Diagnostic accuracy studies (STARD) Statement, 2008).

Recruitment of volunteers and data collection started in Jan 2011 and was completed in December 2011. Recruitment was undertaken by word of mouth and use of fliers with the research objectives placed at the notice board of the research centre at the AECC Bournemouth. Standard demographic data (sex, age) were obtained at the time of recruitment. All normal healthy volunteers who met the inclusion criteria were invited to participate. Their participation was voluntary. Volunteers were free to withdraw from the study if they wanted at any point. Information sheets and consent forms were used to inform and gain consent before they were examined (see Appendices D, E and F).

3.2.1 Subject selection criteria

The following inclusion and exclusion criteria guaranteed selection of a representative group of volunteers for the study objective under consideration. These ensured a homogeneous group of volunteers were recruited and that the study population was sufficiently generalizable (Pocock, 1983).

Inclusion criteria:

- Aged 18 years and above – this age range was selected to be able to evaluate shoulders of subjects below 25 years and over 40 years where different possible stages of tendinopathy/tendon degeneration could be seen (Neer & Welsh, 1977).
- No history of injury, painful episode or surgery – the subject was verbally assessed to confirm that there was no history of injury, recent painful shoulder or surgery.

- No clinical sign of rotator cuff tendon disease – there was no evidence of shoulder pain, signs of rotator cuff impingement or disease.
- No abnormalities on grey-scale ultrasound – no likely abnormality seen on grey-scale ultrasound image.
- Not currently taking part in organized sports > 1x/week, particularly sports known to be associated with supraspinatus tendinopathy (e.g. weight lifting, basketball, volleyball).

Exclusion criteria:

- History of connective tissue injury, metabolic and endocrine diseases – subjects within these categories are prone to have tendon disease.
- Volunteer on steroid or oestrogen medication – these medications are known to be associated with tendon abnormalities (Holmes and Lin, 2006).

3.2.2 Sample selection and data collection

The method of data collection was prospective and consecutive volunteers. Two hundred and eighty four (284) supraspinatus tendons were prospectively examined in a cohort of asymptomatic consecutive Caucasian volunteers (152 men, 132 women; range, 18 years and above) according to the Standards for Reporting of Diagnostic Accuracy (Bossuyt *et al.*, 2003). The volunteers were college students, clinic workers and referred patients who attended the clinic for other investigations that were not shoulder related. Three data sets were collected from each supraspinatus tendon:

- grey-scale grade from the ultrasound image;
- colour grade from the sonoelastogram and;
- strain ratio values.

3.2.3 Sample size calculation

Power and sample size estimations are measures of the number of subjects enrolled in a study. They provide the number of participants required to avoid type I (false positive) and type II (false negative) errors. In a comparative study, “power” refers essentially to the number of subjects required to avoid type II

error. Sample size is more encompassing and is applicable to all types of studies (Jones, Carley & Harrison, 2003).

To determine the number of *controls* (asymptomatic) needed to estimate the specificity of a diagnostic test, the procedure is identical with that described for estimating the number of cases (symptomatic), substituting specificity for sensitivity.

In practice, the clinician will want to estimate both sensitivity and specificity within a study population containing *cases* and *controls*. In this case, to ensure that the study population is representative of the population to which the test will be applied, the proportions of *cases* and *controls* should take account of the prevalence (Prev) of the disease. For the vast majority of diseases, $\text{Prev} < 0.50$, so the number (sample size) of *controls* is greater than number of cases.

In the study, the prevalence of the disease in literature and available data in AECC showed that prevalence is less than 0.50, and therefore the calculated sample size of the *control* (asymptomatic) is more than the sample size of cases (symptomatic) group. This explains why the values are different for the two groups.

Whenever disease prevalence is < 0.50 , an assumption on the expected value of the new diagnostic test sensitivity is made. Also, the minimum acceptable lower confidence limit is specified, together with the required probability (which was set here at 0.95) that this limit is not violated.

Sample Size estimation for Phase 1

The number of subjects used for this study depended on three quantities that were pre-specified by the researcher:

- 1) the width of a CI (clinically acceptable precision);
- 2) the prevalence of the condition or disease in the population of interest, and;
- 3) hypothesized values of sensitivity and specificity.

Null hypothesis – that sonoelastography will not be more than 80% sensitive and 80% specific for detecting tendinopathy.

Step 1

Previous research in supraspinatus tendinopathy using ultrasound and MRI showed very high sensitivity and specificity. To be conservative, this research hypothesizes that the values in the shoulder will be lower.

The selected sensitivity (SN) and specificity (SP) are

SN = 0.80 and SP = 0.80.

A clinically acceptable width of the 95% CIs for sensitivity and specificity was chosen to be no larger than 10%; i.e., a SN from 0.70 to 0.90 and a SP from 0.70 to 0.90. Set $W = 0.10$.

In the AECC, 21.7% of the ultrasound shoulder pathologies (lower range of prevalence) were positive for tendinopathy, i.e., set $P = 0.217$.

To calculate the need for adequate sensitivity, this formula is used (Buderer, 1996; Batavia 2001; Bachmann, ter Riet, Weber & Kessels, 2006):

- $TP + FN = Z^2 \times (SN (1 - SN) / W^2)$
- $N(sn) = TP + FN / P$

($Z = 1.96$; TP = true positive; FN = false negative; CI = confidence interval; P = prevalence).

Step 2

$$TP + FN = 1.96^2 \times 0.8 \times (1 - 0.8) / 0.10^2 = 61.44$$

Step 3

$$N1 = TP + FN/P$$

$$61.44 / 0.217 = 284$$

To calculate the need for adequate specificity, this formula is used:

- $FP + TN = Z^2 \times (SP (1 - SP)) / W^2$
- $N(sp) = FP + TN / (1 - P)$

(FP = false positive; TN = true negative)

Step 4

$$FP + TN = 1.96^2 \times 0.80 \times (1 - 0.80) / 0.10^2 = 61.44$$

Step 5

$$N(sp) = FP + TN / (1 - P)$$

$$N2 = 61.44 / (1 - 0.217) = 78.47$$

Step 6

$N1 > N2$, thus N, rounded to the next higher whole number, is 284 subjects.

3.2.4 Diagnostic ultrasound equipment

The ultrasound scanning machine used the combined autocorrelation method (ECAM) which produced elasticity images with high-speed processing and high accuracy, and achieved a wide dynamic range for strain estimation in tissues. ECAM has the advantage of simple operation that allows the operator to use manual slight compressive force to compress the tissues with the ultrasound linear transducer. This technique is referred to as 'freehand technique', and is easily integrated and desirable for musculoskeletal studies.

The unit has dedicated software with a complex algorithm that has the capability to process in a very short time all the data coming from the lesion as radiofrequency impulses. This minimizes artefacts due to lateral dislocation and allows accurate measurement of the degree of tissue distortion and better spatial resolution (Friedrich-Rust *et al.*, 2007). Tissue elasticity distribution calculation is carried out in real time and displayed in colour superimposed over the grey-scale ultrasound image. The elastographic image is displayed as part of a two panel image with the usual grey-scale ultrasound image on the right side and with the elastography image on the left side. However, one-panel elastographic image can be demonstrated. A ROI for the elastography calculations is manually selected and this includes the targeted area (supraspinatus tendon) and the surrounding tissue (deltoid muscle) as shown in Figure 3.1.

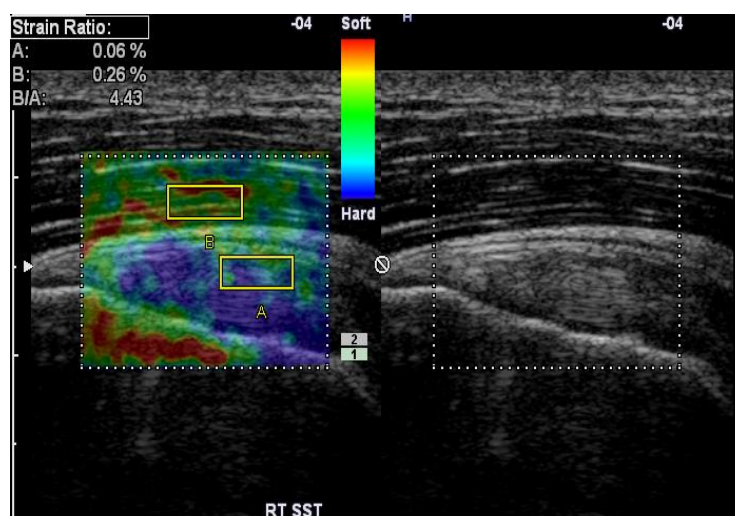


Figure 3.1 An elastogram of a normal supraspinatus tendon of a 26 years old male.

This demonstrates the different colour grades and region of interest (ROI A and B). The strain ratio (B/A) is shown on the upper left of the elastogram; the colour coding indicator or bar and the strain indicator are shown in the middle of the image.

3.2.5 Examination protocol for ultrasound

All volunteers had basic ultrasound examination of the supraspinatus and the greyscale image stored in the cine-memory of the ultrasound machine for analysis. The volunteer's arm was placed posteriorly, and the palmar side of the hand placed on the superior aspect of the iliac wing with the elbow flexed and directed posteriorly. The supraspinatus tendon was evaluated along its long-axis and short-axis. The intra-articular portion of the biceps is used as a landmark to obtain proper transducer orientation for imaging the supraspinatus. The transducer was rotated until the biceps showed as more elongated as possible in the ultrasound image. Then, the probe was shifted upward and posteriorly over the supraspinatus without changing its orientation.

The resulting image was in axis with the supraspinatus (Figures 3.2 and 3.3). Between the supraspinatus and the deltoid, the normal subacromial-subdeltoid bursa appeared as a thin hypoechoic band. The transducer was tilted gently in the area overlying the tendon insertion to avoid anisotropy. Also, the lateral pouch of the subacromial subdeltoid bursa along the lateral edge of the greater tuberosity was scanned. When looking for the supraspinatus on short-axis, the normal cuff must have almost the same thickness from the biceps tendon landmark until 2cm backwards and from this point backwards the tendon seen is the infraspinatus (Martinoli, 2010).

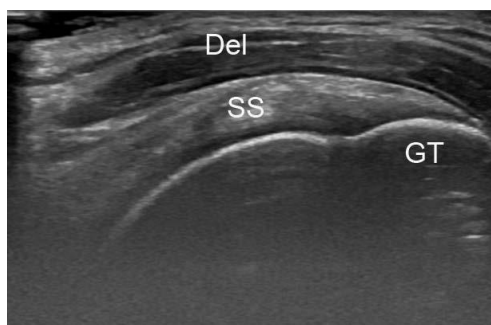


Figure 3.2: Image demonstrating the SST in longitudinal section

SS, supraspinatus tendon; Del, deltoid muscle; GT, greater tuberosity; Left, long axis view (Martinoli, 2010).

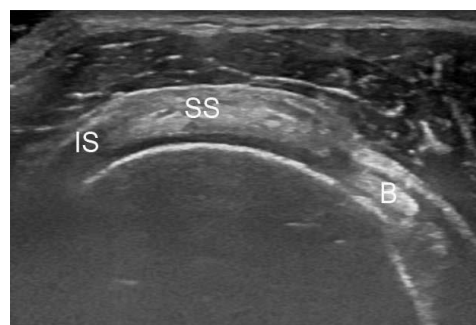


Figure 3.3: Image demonstrating the SST in transverse section

SS, supraspinatus tendon; B, biceps tendon; IS, infraspinatus Right, short axis view (Martinoli, 2010).

3.2.6 Examination protocol for sonoelastography and strain ratio measurements

Each supraspinatus tendon of every volunteer was examined two times by the author in longitudinal section similar to the ultrasound technique in section 3.2.5 by applying light repetitive compression with the hand-held transducer over the shoulder. The probe made light skin contact, and gentle compressions were applied to give continuous, reproducible colour display. A pressure scale reading of 3 or 4 (or a display that is flashing between 2/3/4/5) was achieved to obtain a reproducible stable colour display. The image was frozen and scrolled back to find the best still frame that represented optimum reading.

For the purpose of this study, the supraspinatus tendon was imaged in the longitudinal plane. The longitudinal section of the tendon appeared in a horizontal position on the screen, with the deltoid muscle anterior to it, and a cross section of the biceps tendon to the right. The sonoelastogram is shown within a rectangular ROI as a colour-coded, real-time image that is superimposed on the grey-scale ultrasound image. The colour-code represents the relative stiffness of the tissues of the sonoelastogram. The supraspinatus tendon and the deltoid muscle are seen within the ROI. For strain ratio measurement, two boxes of the ROI are superimposed on the tendon (ROI A) and the deltoid (ROI B). These two regions were used by the ultrasound machine to calculate the strain ratio B/A.

3.2.7 Data recording

The images and data were automatically recorded and stored in the ultrasound scanner data memory. This electronic storage allowed them to be coded and anonymised before being stored. The identities of the volunteers were not revealed. All data collected were deleted from the ultrasound machine memory after the completion of the study. The subjects were to be informed of the study findings if they wished.

3.2.8 Statistical tests and method of analysis

(a) Visual inspection of the supraspinatus tendon to determine grey-scale ultrasound and sonoelastographic patterns:

The grey-scale ultrasound patterns were evaluated using Archambault *et al.*, (1998) grading system.

- Grade 1: normal-appearing tendon (smooth margins, homogeneous echotexture);
- Grade 2: enlarged tendon (homogeneous echotexture, hypoechogenicity);
- Grade 3: hypoechoic area with/without tendon enlargement, or with calcification.

Grade 1 tendons represent normal tendon, and Grades 2 and 3 tendons represent abnormal or pathologic tendon.

The sonoelastography appearances were evaluated using an experimentally proven colour grading system (Frey, 2003).

- Grade 1: if the tendon was blue/green (hard tissue);
- Grade 2: yellow colour evident within the tendon (intermediate tissue or mild softening);
- Grade 3: red colour evident within the tendon (soft tissue).

(b) Results of normal ultrasound and sonoelastography patterns were analysed. Distribution of the percentages of males, females and combined elastographic grades and the distribution of the sonoelastographic colour grade percentages in males, females and both were demonstrated using bar charts. Demographic data and standard descriptive statistics of sonoelastographic pattern were carried out including gender distribution with standard deviations. Mean elastographic SR values of males and females and combined strain ratio values were carried out on the data and demonstrated using box plots and histograms. An independent samples *t-test* was conducted to compare the strain ratio values of males and females. Statistical significance was defined as a two-sided $p \leq 0.05$ (Pallant, 2007). The measure of agreement between ultrasound and sonoelastography was assessed using *kappa* measure of agreement. All statistical parameters were calculated using the Statistical Package SPSS 20.0 (SPSS Inc., Chicago, Ill, USA).

3.3 Results

3.3.1 Demographic data and standard descriptive statistics of US pattern

There were 152 males (53.5%) and 132 females (46.5%) in the sample of 284 supraspinatus tendons as shown in Table 3.1. The age range was between 20 and 58 years with a mean of 29.9 years and a standard deviation of ± 9.5 years.

Table 3.1: Ultrasound grade versus gender distribution.

Grade		Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F	
Ultrasound	1	147 (51.8%)	125 (44.0%)	272 (95.8%)
	2	5 (1.7%)	7 (2.5%)	12 (4.2%)
	3	0	0	0
Total		152 (53.5%)	132 (46.5%)	284 (100%)

The US pattern of the tendons was very easily visible and showed a characteristic homogeneous, mid-grey echotexture with normal fibrillar echopattern and no evidence of obvious hypoechoic areas or calcifications in 272 (95.8%) tendons. This pattern corresponded to Grade 1 pattern indicating normal, hard tissue appearance (Figure 3.4). A total of 12 (4.2%) tendons showed evidence of enlargement in keeping with Grade 2 grading pattern. No tendon demonstrated any evidence of calcification within. Therefore, no tendon demonstrated Grade 3 pattern. The results also showed that a total of 147 (51.8%) tendons of males and 125 (44.0%) tendons of females demonstrated Grade 1 colour pattern. Grade 2 colour pattern was demonstrated in 5 (1.7%) male tendons and 7 (2.5%) female tendons. This shows that more males presented with normal tendons than females. The grade 2 findings indicate that ultrasound showed evidence of tendon softening in otherwise asymptomatic participants.

Grade 1 and grade 2 ultrasound patterns are shown in Figure 3.4 and Figure 3.5 respectively demonstrating their characteristic patterns.

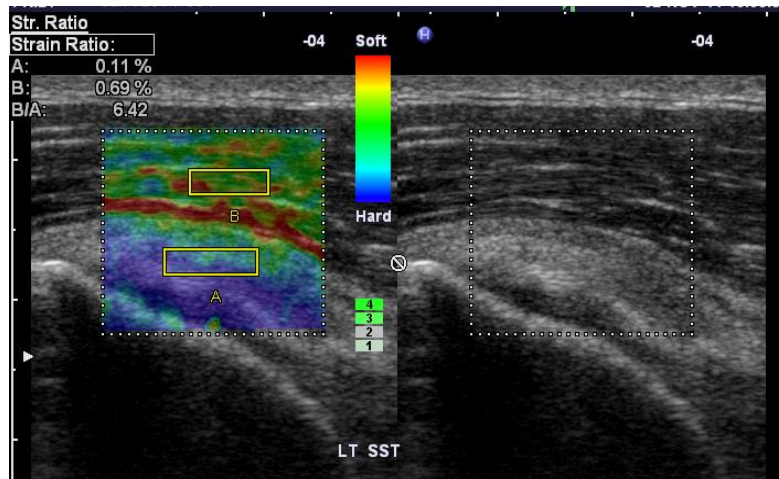


Figure 3.4: A longitudinal view of normal (Grade 1) left supraspinatus tendon.

The image in Figure 3.4 shows a sonogram in the right half of the image which shows uniform, mid-grey echotexture of the supraspinatus tendon with normal fibrillar echopattern consistent with Grade 1 pattern. The elastogram in the left half of the screen shows how the two patterns compare.

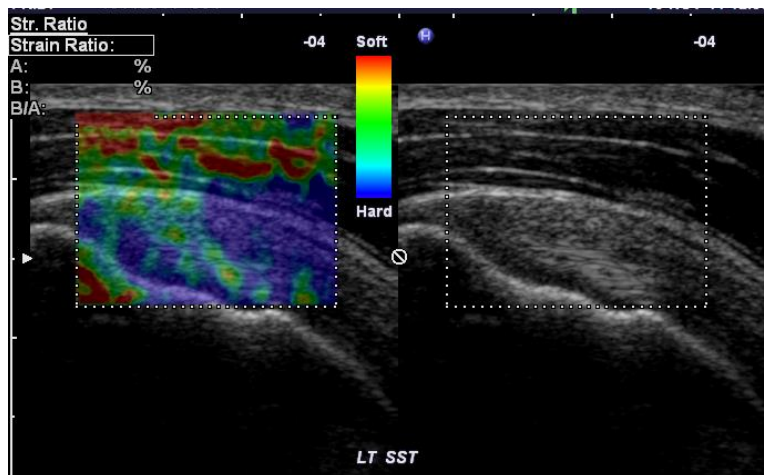


Figure 3.5: A longitudinal view of Grade 2 left supraspinatus tendon.

The image in Figure 3.5 shows a sonogram in the right half of the image which shows mildly swollen supraspinatus tendon consistent with Grade 2 pattern. The elastogram in the left half of the screen shows how the two patterns compare.

The distributions of the percentages in Table 3.1 are shown in the bar charts in Figure 3.6 and Figure 3.7.

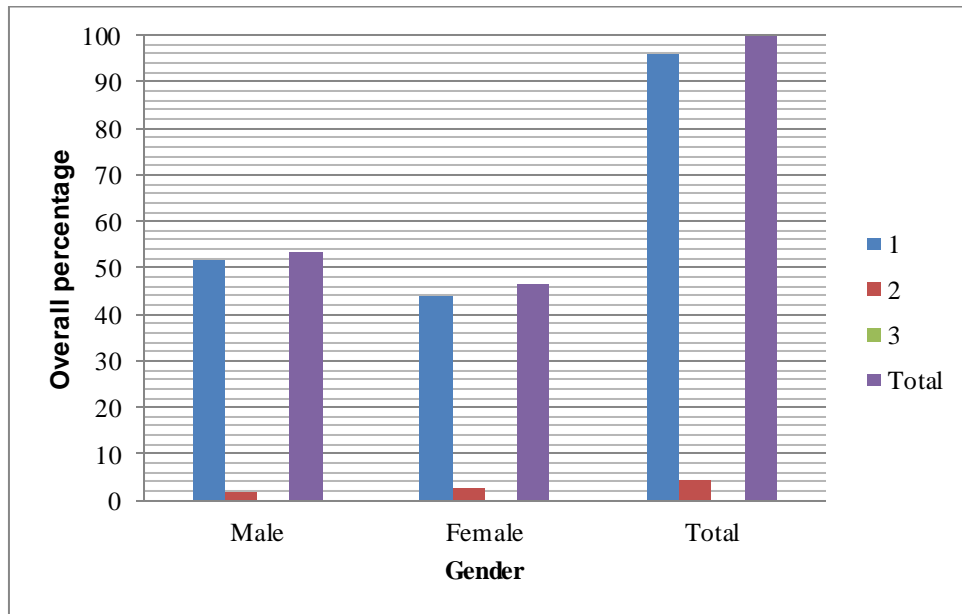


Figure 3.6: Distribution of the percentages of males, females and combined ultrasound grades.

Bar chart of overall ultrasound grade percentages and gender showing the distribution of the percentages of males, females and combined ultrasound grades (1 = ultrasound grade 1; 2 = ultrasound grade 2; 3 = ultrasound grade 3).

The bar chart of Figure 3.7 shows all the overall percentages of all the males, females and both genders combined in grades 1, 2, 1nd 3 and their total.

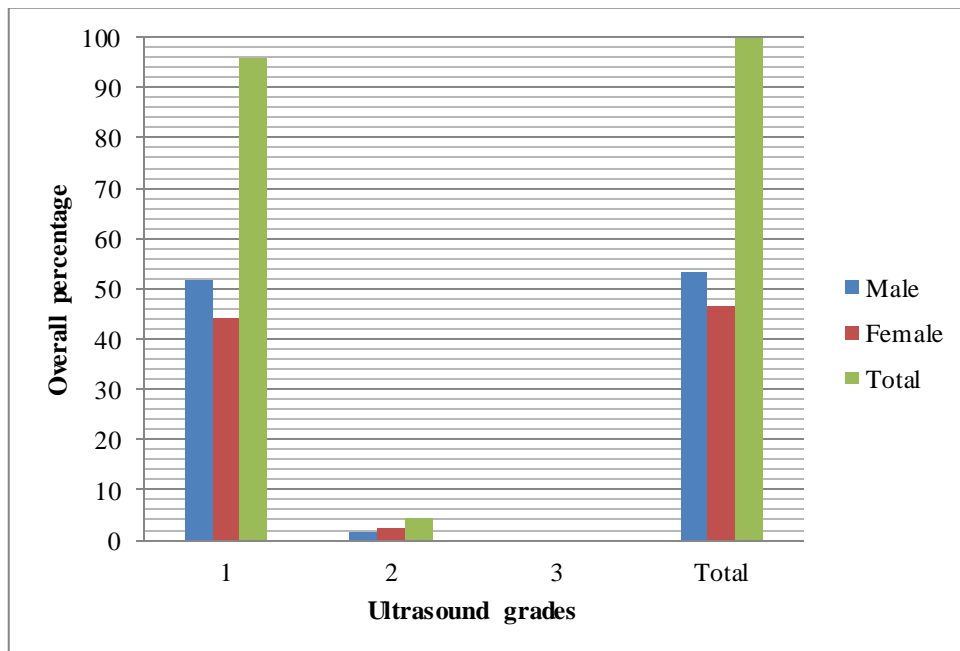


Figure 3.7: Distribution of the ultrasound grade percentages in males, females and both.

Bar chart of overall gender percentages and ultrasound grades showing the distribution of the ultrasound grade percentages in males, females and both (1 = ultrasound grade 1; 2 = ultrasound grade 2; 3 = ultrasound grade 3).

3.3.2 Demographic data and standard descriptive statistics of sonoelastography pattern

The results presented sonoelastograms and strain ratio values of the supraspinatus tendons of normal volunteers.

Table 3.2: Sonoelastography grade versus gender distribution.

Grade		Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F	
Sonoelastography	1	130 (45.8%)	114 (40.1%)	244 (85.9%)
	2	22 (7.8%)	18 (6.3%)	40 (14.1%)
	3	0	0	0
Total		152 (53.5%)	132 (46.5%)	284 (100%)

The tendon elastographic pattern was very easily visible. The tendons showed a characteristic blue-green pattern predominantly. This was evident in 244 (85.9%) tendons as shown in Table 3.2. This pattern corresponded to Grade 1 colour grading pattern, indicating normal, hard tissue appearance of the supraspinatus tendon. It is important to state that the mixture of green / blue colouration varied from subject to subject. In most subjects it was predominantly blue and less of green colour (Figures 3.8 and 3.9).

A total of 40 (14.1%) tendons showed evidence of yellow colouration within the tendons in keeping with Grade 2 colour grading pattern. This is an indication of intermediate tissue thickness. These colour patterns are shown in the supraspinatus elastogram on the left side of the image in Figure 3.8. No tendon showed evidence of red colouration as seen in Grade 3 grading pattern. A total of 130 (45.8%) males and 114 (40.1%) females showed Grade 1 colour grade. Grade 2 colour grade pattern was demonstrated in 22 (7.8%) males and 18 (6.3%) females (Table 3.2, Figure 3.8 and Figure 3.9).

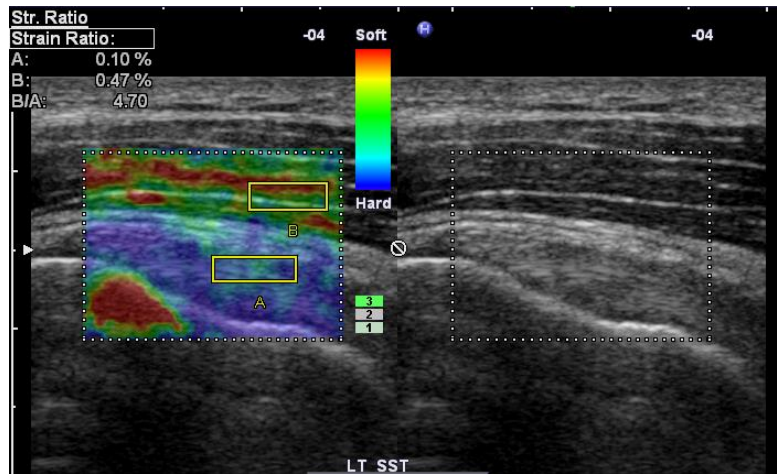


Figure 3.8: An elastogram and grey scale ultrasound appearance of normal supraspinatus tendon.

The image in Figure 3.8 shows the different colour grades and regions of interest (ROI A and B; the ROI are taken from the supraspinatus tendon and deltoid muscle to calculate the strain ratio). The supraspinatus tendon showed predominant blue and inter-shades of green consistent with a Grade 1 colour pattern (Frey, 2003; De Zordo *et al.*, 2009a, De Zordo *et al.*, 2009b). The strain ratio (B/A) is shown on the elastogram; the colour coding indicator or bar and the strain indicator are shown in the middle of the screen. On the right hand of the screen is a grey scale US image of the same supraspinatus tendon demonstrating a characteristic homogeneous, mid-grey echotexture with normal fibrillar echopattern in keeping with Grade 1 ultrasound pattern. Elasticity spectrum shown was between red, representing soft tissue, and blue, representing hard tissue; green and yellow in-between, as represented by the colour bar in the middle of the image in Figure 3.8.

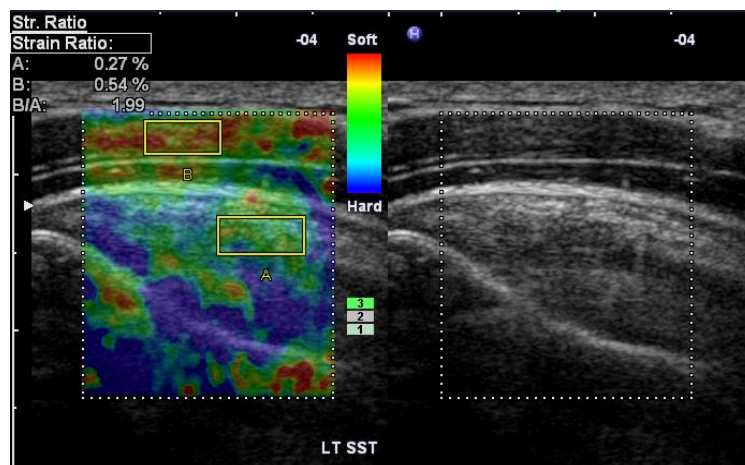


Figure 3.9: An elastogram of a Grade 2 supraspinatus tendon.

The image in Figure 3.9 shows patches of yellow coloration near the bursal and articular surfaces of the thickened supraspinatus tendon. This is consistent with softening in these portions of the tendon consistent with abnormal tendon.

The distributions of the percentages in Table 3.2 are shown in the bar charts in Figure 3.10 and Figure 3.11. The bar chart of Figure 3.10 shows the overall percentages of grades 1, 2, 3 and their total in all the males, females and both genders combined.

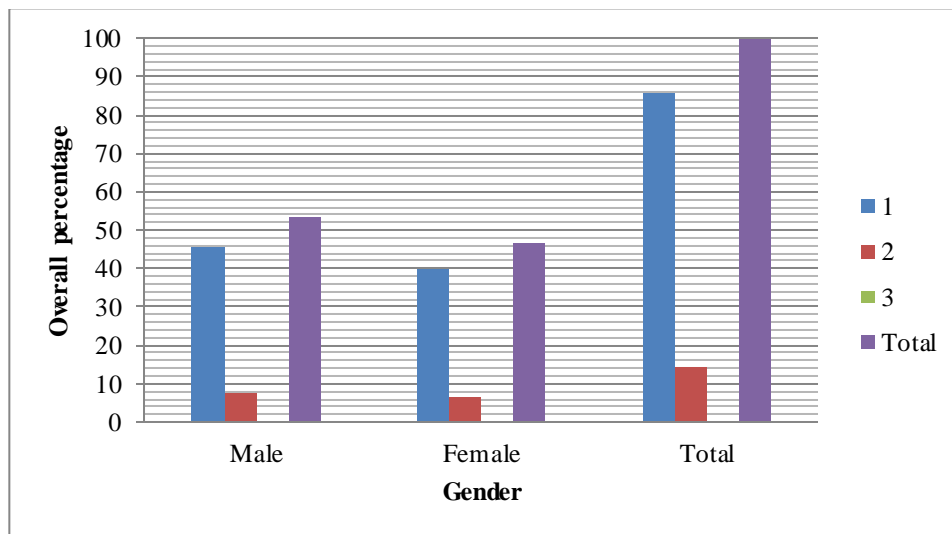


Figure 3.10: Distribution of the percentages of males, females and combined sonoelastography grades.

Bar chart of overall sonoelastography grade percentages and gender showing the distribution of the percentages of males, females and combined sonoelastography grades (SE 1 = sonoelastography grade 1; SE 2 = sonoelastography grade 2; SE 3 = sonoelastography grade 3).

The bar chart of Figure 3.11 shows the overall percentages of all the males, females and both genders combined in grades 1, 2, 3 and their total. In Figure 3.11 no Grade 3 tendon was recorded and therefore no bar chart is given.

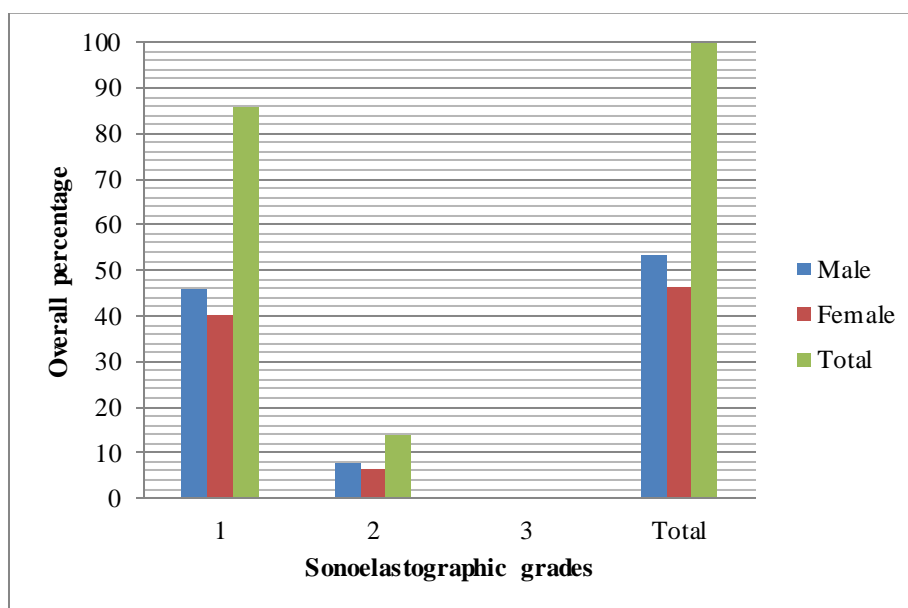


Figure 3.11: Distribution of the sonoelastography colour grade percentages in males, females and both.

Bar chat of overall gender percentages and sonoelastography grades showing the distribution of the sonoelastography colour grade percentages in males, females and both (SE 1 = sonoelastography grade 1; SE 2 = sonoelastography grade 2; SE 3 = sonoelastography grade 3).

3.3.3 Results of strain ratio values

The mean strain ratio was calculated as a mean of the individual strain ratio values of all 284 participants in phase 1 study ranging from 1.6 to 10.70 using standard descriptive statistics. The mean strain ratio value in the asymptomatic group was 5.55 with a standard deviation of ± 1.24 .

3.3.4 Mean elastographic strain ratio values

Table 3.3: Mean elastographic strain values of males and females.

Sex	N	SR Mean	Min	Max	Range	Std. Deviation
Male	152	5.71	0.90	27.70	26.80	± 1.44
Female	132	5.36	0.90	52.20	51.30	± 0.92
Total	284	5.55	0.90	52.20	51.30	± 1.24

(SR = strain ratio; N = number)

The distribution of the mean strain values of all participants is shown in the histogram in Figure 3.12. The mean strain values of both sexes show that the strain values in males are slightly higher than that of females giving values of 5.7

± 1.44 (0.90 – 27.70) and 5.4 ± 0.92 (0.90 – 52.20) respectively as shown in Table 3.3, and in the histograms of Figures 3.12 and 3.13.

Table 3.4: Summary of normal mean SR indices.

Mean strain values	Number	Group
5.6 (± 1.24 SD)	284	All
5.7 (± 1.446 SD)	152	Males
5.4 (± 0.92 SD)	132	Females

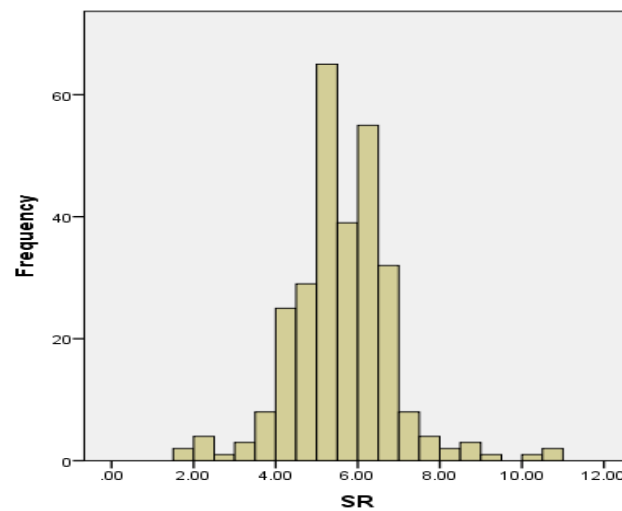


Figure 3.12: Histogram of the frequency of the mean strain indices of all volunteers (SR – strain ratio).

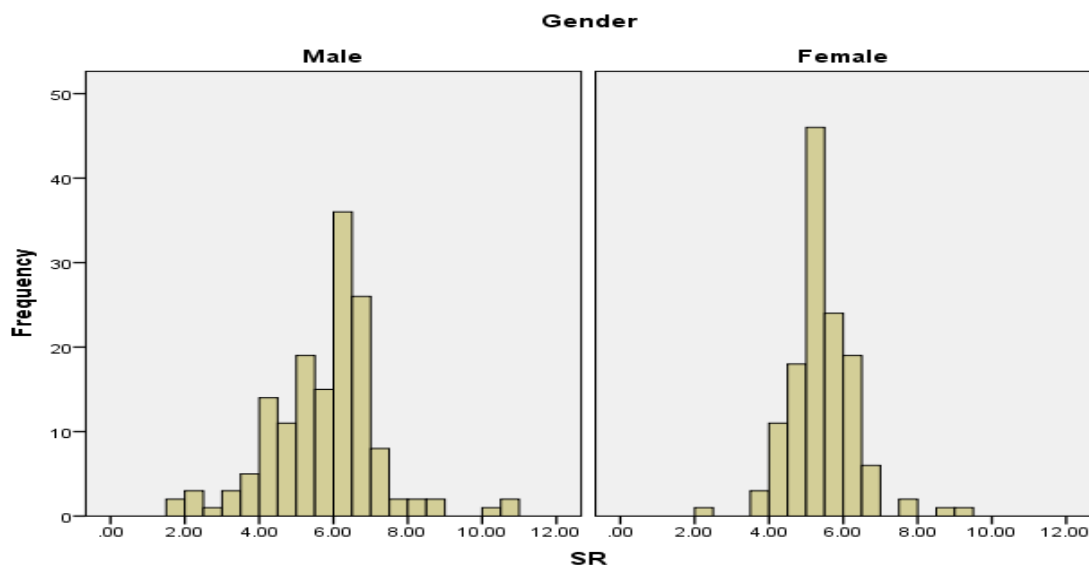


Figure 3.13: Histogram of the frequency of the mean strain indices of male and female.

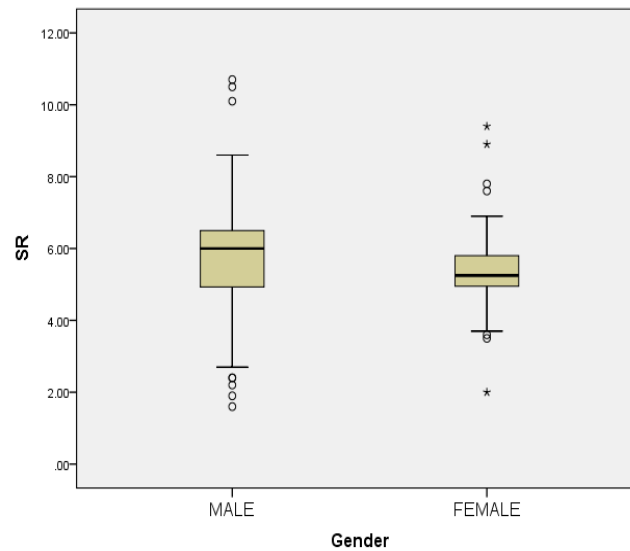


Figure 3.14: Distribution of the mean strain ratio values for male and female supraspinatus tendons.

Individual boxplot mean strain ratio values for males and female supraspinatus tendons are shown in Figure 3.14. The boxplots are useful when comparing the distribution of mean strain values in males and females. The length of the box is the interquartile range (IQR) of each variable and 50% of strain ratio readings fall within the IQR for both sexes. This means that the IQR is wider for males than females, indicating greater spread. The median strain ratio of males is higher than that of females. The whiskers indicate the smallest and largest values of each variable. It is also easy to see that the male values have the smallest and largest strain ratio values.

Combined box plot mean strain ratio values for males and female supraspinatus tendons are shown in Figure 3.15. The distribution of the mean of sonoelastographic strain ensures no violation of the assumption of normality (test

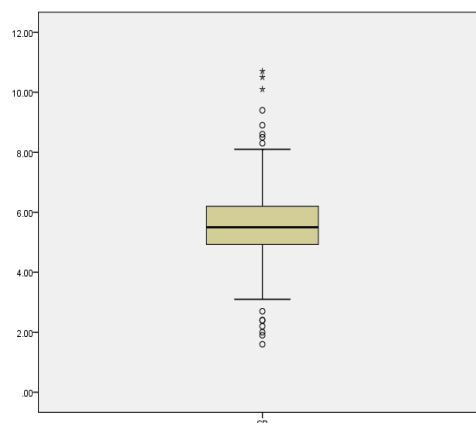


Figure 3.15: Distribution of the mean strain value for all the participants.

of normality using Kolmogorov-Smirnov statistic of 0.000, $p = 1.000$). The box-

plot shows the interquartile range lay at 5.30–5.70 strain values and the mean has a value of 5.55.

There were outliers and extreme values in the box-plot represented by little circles and asterisk respectively. These are consistent with tendons with high strain values which tend to have high calcium content or fibrotic change as seen in calcific tendinopathy.

3.3.5 Association between strain ratio of male and female supraspinatus tendons

To find out whether there is a significant difference between male and female groups, an independent samples *t*-test was conducted to compare the strain ratio values of males and females. There was statistically significant difference in values for males ($M = 5.71$, $SD = 1.44$) and females ($M = 5.36$, $SD = 0.92$); $t(282) = 2.35$, $p = 0.02$ (two-tailed). The magnitude of the differences in the means (mean difference = 0.34, 95% CI: 0.06 to 0.63) was small (eta squares = 0.02). The guidelines proposed by (Cohen 1988, pp. 284-287) for interpreting this value are: 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

3.3.6 Measure of agreement between ultrasound and sonoelastography

It is important to ascertain if there is a relationship between ultrasound appearances and sonoelastographic values. The consistency of the two different diagnostic tests, ultrasound and sonoelastography, in classifying the supraspinatus tendons as normal and abnormal, is assessed using *kappa* measure of agreement. The *kappa* measure of agreement is a non-parametric test which requires two categorical variables and equal number of categories (normal tendon = 1, abnormal tendon = 2). It assumes equal number of categories from the two tests. The aim here is to see if the tendons classified as normal using ultrasound were also classified as normal using sonoelastography.

Table 3.5: Cross tabulation of US and SE to demonstrate *kappa* measure of agreement.

		Sonoelastography	
		1	2
Ultrasound	1	255(89.7%)	12 (4.2%)
	2	0 (0%)	17 (6.1%)

Both grey-scale ultrasound and sonoelastography agree that 89.7% are normal or positive, and while ultrasound showed 4.2% to be positive, sonoelastography demonstrated them as negative as shown in Table 3.5. Both modalities did not agree on 4.2% of cases - false positive of 0 (0%), and false negative of 4.2%. True negative is 6.1%.

From the data above, the *kappa* measure of agreement value is 0.42 with a significance value of $p < 0.0005$. According to Peat (2001, p.228) a value of 0.5 for *kappa* = moderate, > 0.7 = good agreement, and > 0.8 = very good. Therefore 0.42 is moderate agreement.

Also, a chi-square test for independence (with Yates continuity correction), indicated that the appearance of grey-scale ultrasound is not significantly different from that of sonoelastography, $X^2 (1, n = 284) = 0.31, p = 0.15, phi = -0.85$.

There was a strong positive correlation between grey-scale ultrasound and sonoelastography, $R = 0.52, n = 284, p = 0.0005$.

Table 3 6: Summary table of ultrasound versus sonoelastography.

		Ultrasound			Sonoelastography		
		Gender <i>n</i> (%)		Total <i>n</i> (%)	Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F		M	F	
Grade	1	147 (51.8%)	125 (44%)	272 (95.8%)	130 (45.8%)	114 (40.1%)	244 (85.9%)
	2	5 (1.7%)	7 (2.5%)	12 (4.2%)	22 (7.8%)	18 (6.3%)	40 (14.1%)
	3	0	0	0	0	0	0
Total		152 (53.5%)	132 (46.5%)	284 (100%)	152 (53.5%)	132 (46.5%)	284 (100%)

Deduction from results in the summary Table 3.6 above showed that sonoelastography demonstrated 28 abnormal tendons (Grade 2) which were missed by conventional ultrasound and classified as normal. This represented 9.9% of the population studied.

3.3.7 Summary of findings

The tendons of normal volunteers on grey scale ultrasound showed a characteristic homogeneous, mid-grey echotexture with normal fibrillar echopattern with no evidence of obvious hypoechoic areas or calcifications in 272 (95.8%) tendons. This pattern corresponded to Grade 1 pattern indicating hard tissue (normal) appearance. A total of 12 (4.2%) tendons showed evidence of enlargement of the tendons in keeping with Grade 2 pattern or abnormal tendon appearance. On sonoelastography, tendons of normal volunteers showed a characteristic blue-green pattern predominantly evident in 244 (85.9%) tendons. This pattern corresponded to Grade 1 colour pattern and it is an indication of hard tissue appearance of the supraspinatus. The mixture of green/blue colouration varied from subject to subject. In most subjects it was predominantly blue and less of green colour. Evidence of yellow colouration within the tendons was seen in 40 (14.1%) tendons in keeping with Grade 2 colour pattern indicating intermediate tissue thickness. There was no evidence of red colouration (grade 3 colour pattern). The results showed that sonoelastography demonstrated 28 abnormal tendons which were not seen in conventional ultrasound. This represented 9.9% of the population studied.

Results showed that more males presented with normal tendons than females. A chi-square test showed that there is no association between gender and tendon grade (CS = 0.708, $p = 0.400$).

The *kappa* measure of agreement value is 0.42 ($p < 0.0005$) indicating moderate agreement. Also, a chi-square test indicated that the appearance of ultrasound is not significantly different from that of sonoelastography, $X^2 (1, n = 284) = 0.31$, $p = 0.15$, $\phi = -0.85$. There was a strong positive correlation between ultrasound and sonoelastography, $r = 0.52$, $n = 284$, $p = 0.0005$.

The mean strain for normal supraspinatus tendons was 5.6 ($\pm 1.24SD$). There was a slight difference in the mean strain ratio for males and females with the mean being slightly higher in males (5.7 $\pm 1.44SD$) than in females (5.4 $\pm 0.92SD$). There was statistically significant difference in the mean strain ratio values for males and females.

In conclusion the findings of this Phase 1 group have provided the mean strain value for normal tendons

3.4 Discussion

This section has been structured into five categories and subsections. It begins with an evaluation of how this study fits with outcomes of different studies and a review of various sample sizes of other studies. A section on identification of 'at risk' tendinopathic cases with detection of subclinical changes in tendons have been presented in this section. This section noted gender variations as well as disparity in image appearance, technique and compressibility of sonoelastography. It concludes by discussing strain ratio tool and the size of the ROI window.

3.4.1 Demographic findings

The supraspinatus tendon is commonly injured and affected by tendinopathy (Lalitha, Reddy & Reddy, 2011). According to Starr and Kang (2001), supraspinatus tendinopathy is the most common cause of shoulder pain. It is the most frequently affected tendon in patients with shoulder pain. A paper on 'The sonographic study of painful shoulder' by Iagnocco, Coari, Leone & Valesini, (2003) identified the supraspinatus tendon as the most often involved tendon in the shoulder (64%), followed by the long head of biceps (48.1%) and the acromioclavicular joint (51.5%). This underlines the reason for this study on the supraspinatus tendon. As real-time sonoelastography is an established method for measuring tissue elasticity, the supraspinatus tendon is visualized as a hard structure. This study confirmed the hard tendon structure as colour grade 1 ranging from blue to green according to an established colour grading pattern (Frey, 2003). This was seen in 85.9% of the tendons. This finding reflects the literature evidence of components of tendon that define its hard structure. In line with this, O'Brien (2005) demonstrated the tendon as consisting of typical parallel bundles of type I collagen called tropocollagen. This composition of type I fibres include collagen (30%) and elastin (2%) that are implanted in an extracellular matrix of mucopolysaccharides and a proteoglycan gel which contains water (68%) and tenocytes. Another author, Kannus (2000) contributed that elastin

adds to the tendon flexibility while the protein tropocollagen forms the mass of the dry weight of the tendon totalling about 65-80%.

In the current study, sonoelastography showed soft tendon structure in 14.1% and US demonstrated 4.2% of grade 2 pattern in the volunteers though there was no evidence of symptoms of tendinopathy. These findings can be interpreted as subclinical. Follow-up of these volunteers were recommended to ascertain if the findings resolved or if they became symptomatic. The rest of the volunteers showed normal findings on ultrasound.

When sonoelastography was compared with grey-scale ultrasound, a strong positive correlation ($r = 0.52$) was obtained when hard structure of grade 1 was defined as normal. Both modalities agreed that 89.7% (244) are normal or positive, and did not agree on 4.2% of cases - false positive of 0 (0%), and false negative of 28 (4.2%). The *kappa* value showed moderate agreement ($k = 0.42$, $p < 0.0005$) and a chi square test for independence indicated that the appearance of grey-scale ultrasound was not significantly different from that of sonoelastography. In the same vein, a previous study by De Zordo *et al.* (2009a) demonstrated a perfect correlation ($r = 1$) when the accuracy of sonoelastography was compared with ultrasound on the study on Achilles tendon. However, further histological correlation would be desirable.

The current study used a sample size of 284 supraspinatus tendons. This sample size is large in contrast to other published studies in tendons. In the studies by De Zordo *et al.* (2009) and De Zordo *et al.* (2008) on the common extensors (CEO) tendons in the elbow and on the Achilles tendon respectively, 44 CEO tendons and 25 Achilles tendons were investigated respectively. Two larger studies on Achilles tendons by De Zordo *et al.* (2009b) and Klauser, De Zordo & Faschingbauer (2009) used 80 tendons each, while the study by Drakonaki, Allen & Wilson (2009) used 50 Achilles tendons. A study that used similar supraspinatus tendon as the current study was carried out by Abdel Razek & Ezzat (2008), and the study sample size was 20. These are summarized in Table 3.7. A thorough reflection of the above shows that the current study remains one of the studies with the largest sample size in tendon

studies. The implication is that statistically a larger sample size increases the chance of finding a significant

Table 3.7: Comparison of sample size with other studies.

Authors	Body part
De Zordo <i>et al.</i> , 2007	50 Achilles tendons in 25 healthy sex age matched volunteers.
De Zordo <i>et al.</i> , 2008	Achilles tendon of 25 healthy volunteers.
Abdel Razek & Ezzat, 2008	20 healthy volunteers and 40 patients presenting with shoulder pain.
De Zordo <i>et al.</i> , 2009a	CEO tendons (lateral epicondyles) of 44 asymptomatic elbows of 28 healthy volunteers.
De Zordo <i>et al.</i> , 2009b.	80 asymptomatic Achilles tendons of 40 healthy volunteers.
Drakonaki, Allen & Wilson, 2009	50 normal Achilles tendons were prospectively examined using RTE.
Klauser, De Zordo and Faschingbauer, 2009	80 Achilles tendons in healthy volunteers and 25 tendons in patients complaining of inflammation and pain in the Achilles region.
De Zordo <i>et al.</i> , 2010	Achilles tendons in 25 consecutive patients with chronic Achilles tendinopathy and 25 healthy volunteers were examined clinically by US and by SE.
Ohuegbe, 2014 (thesis)	Supraspinatus tendons of 284 healthy volunteers and 204 patients with shoulder pain and symptoms of supraspinatus tendinopathy.

difference when it actually exists, and this is because it reflects the population mean more reliably (Biau, Kerneis & Porcher, 2008). This in effect confers validity to the present study.

3.4.2 Identifying the ‘at risk’ tendinopathy

The results showed that sonoelastography demonstrated supraspinatus tendons with mild softening which were not seen on ultrasound. This represented 9.9% of the volunteers and could represent very early signs of subclinical alterations or early pathologic changes in the supraspinatus tendons. This means that sonoelastography was more sensitive than ultrasound in detecting alterations in

tendon characteristics which would otherwise have gone unnoticed. It could also mean that sonoelastography was simply too sensitive or that it could represent false-positive findings. This fact has been confirmed in several studies on other tendons by other authors as shown in Table 3.8. The results showed 4% in common extensor origins tendon in the elbow (De Zordo *et al.*, 2009a), 7% in Achilles tendon (De Zordo *et al.*, 2008), 16% at mid-portion and 4% at proximal third of Achilles tendon (De Zordo, 2007), 12.1% (De Zordo *et al.*, 2009b), and 7% of Achilles tendon (De Zordo *et al.*, 2010). It was recommended that these volunteers have a follow-up examination.

The findings of this study do not imply that the percentage is in the mid-range of two studies by De Zordo *et al.* (2009b, 2010) as the results are got from different tendons and the figures are relative to the peculiar study and coincidental.

The significance of this finding was that it can be used to emphasize the importance of sonoelastography in showing that imaging appearances did not particularly reflect clinical symptoms and diagnosis. The results indicate that these normal tendons could have underlying pathology.

This therefore implies that finding becomes important as it would determine the management pathway for such 'patients' On the other hand, if these 'patients' are left untreated, they could be followed-up to see if they would develop tendinopathy.

Another example was also seen in a longitudinal study of the patellar and Achilles tendons by Fredberg & Bolvig (2002). Their study was carried out on football players using ultrasound and it showed that tendon changes can be diagnosed before they become symptomatic (Fredberg & Bolvig, 2002). A thorough reflection of the above demands one to embrace the claim by Klauser & Peetrans (2010) that tendon softening can be used to identify the 'at risk' supraspinatus tendinopathy. The claim can be used to emphasize the importance of other similar studies where imaging appearances did not particularly reflect clinical symptoms and diagnosis as shown in studies by Peers & Lysens (2005) and Richards, Win & Jones (2005).

Table 3.8: SE detection of subclinical changes in tendons.

Authors	Body part	Results
De Zordo <i>et al.</i> , 2007	50 Achilles tendons in 25 healthy sex age matched volunteers.	Grade 2 change was found in 16% at mid-portion and in 4% at proximal tendon thirds.
De Zordo <i>et al.</i> , 2008	Achilles tendon of 25 healthy volunteers.	Normal findings were present in 100% of clinical examinations, in 100% of US images and in 93% of SE images (and mild alterations in 7%).
De Zordo <i>et al.</i> , 2009a	CEO tendons (lateral epicondyles) of 44 asymptomatic elbows of 28 healthy volunteers.	Hard tendon structures in 96% of tendon thirds and mild alterations in 4%.
De Zordo <i>et al.</i> , 2009b	80 asymptomatic Achilles tendons of 40 healthy volunteers.	Mild softening was found in 12.1% of the tendons.
De Zordo <i>et al.</i> , 2010	25 patients with chronic Achilles tendinopathy and 25 healthy volunteers.	Mild softening was found in 7 % of the healthy volunteers.
Ohuegbe, 2014 (thesis)	Supraspinatus tendons of 284 healthy volunteers and 204 patients with shoulder pain.	Current study showed 9.9% of mild alterations.

(All the studies used same type of equipment and transducer frequency - Hitachi, 6-13MHz).

This becomes important as it would determine the management pathway for such 'patients'. Fredberg *et al.*, (2004) proposed the solution where tendon load could be reduced before tendinopathic symptoms became evident, and treatment to be commenced before the condition became chronic.

However, there are still unanswered questions regarding this finding. This is because there is still a gap to fill in the area of predictive information regarding the development of tendinopathy. Klauser & Peetrans (2010) was of the opinion that further future studies are required to investigate this gap and sonoelastography, because of its capacity to define quantitative tissue characteristics, would be used. Another area of potential research is to assess if sonoelastography could be used as a screening tool which would allow athletes to modify their exercise model to prevent tendon damage.

3.4.3 Gender and age variations

Though more males presented with normal tendons than females, there was statistically significant difference in values for males ($M = 5.71$, $SD = 1.44$) and females ($M = 5.36$, $SD = 0.92$); $t(282) = 2.35$, $p = 0.02$ (two-tailed). However, a chi-square test showed that there was no association between gender and tendon grade in the current study ($X^2 = 0.708$, $p = 0.400$). This finding was corroborated by a study on Achilles tendon by Drakonaki, Allen & Wilson (2009). Their study showed that there was no statistically significant correlation between the tendon groups and sex (X^2 test, $X^2 = 1.20$, $p = 1.23$).

Also, there was no correlation between sonoelastographic appearances of the supraspinatus tendon and age or gender in the current research. In their study, Drakonaki and colleagues (2009) demonstrated that there was no significant difference in age between the two groups (t -test, $t = 1.25$, $p = 0.67$). This finding agrees with the results of this current study.

Reports from other authors in the biomechanics of viscoelastic properties of tendons have shown that these properties contrast between individuals, probably depending on age, sex, and level of physical activity (Kubo, Kanehisa & Fukunaga, 2002; Kubo, Kanehisa & Fukunaga, 2003; Babic and Lenarcic, 2004). However, these findings were noted in Achilles tendons but are yet to be confirmed in supraspinatus tendons and may need further multicentre trials to do so.

3.4.4 Image appearance, technique and compressibility

The results of the current study demonstrated that sonoelastography of the supraspinatus tendon is a practicable method where sonoelastograms could be easily analysed. The colour codes were easy to define within the sonoelastograms, and the regions that showed softening in the tendons were readily discernible. Superimposition of colour on the ultrasound image allowed easy comparison with the adjacent ultrasound image on the split screen. The boundary between the deltoid muscle and the tendon was clear to demarcate.

The technique used in this study was simple freehand technique. This technique was used in several studies involving sonoelastography of different tendons as

shown in the studies by Hussain (2008), Drakonaki, Allen & Wilson (2009) and De Zordo *et al.* (2011). In the current study, as also demonstrated in the study by Drakonaki and colleagues (2009) on the Achilles tendon, the longitudinal image of the tendon was used in preference to the transverse image. The longitudinal image was more reproducible, convenient and easier to achieve due to the curvature of the shoulder. Another reason is that it was easier to demonstrate supraspinatus tendon pathologies in long axis than transverse views as image inhomogeneity and artefact such as anisotropy were less seen in longitudinal projections. Though image inhomogeneity is seen as a limitation, Drakonaki, Allen & Wilson (2009) argued that inhomogeneity in tendon elastograms could be as a result of differences in the mechanical properties among tissue components in a normal tendon which was likely to represent a sub-clinical disease condition within the tendon. In agreement with the limitations of transverse images, strain distribution could be less uniform in the lateral edges in a transverse section as the tendon appears to demonstrate a curved appearance at these edges and there could be non-uniform operator pressure at the edges. Many authors listed non-axial compression movements of the operator's free hand as a major limitation in the study of the breast (Hiltawsky *et al.*, 2001; Abdullah, Mesurolle, El-Khoury & Kao, 2009), and in the patellar tendon (Drakonaki, Allen & Wilson 2009). Using a stand-off pad would permit better contact between the skin and probe but the present study did not use it as it is not routine practice in shoulder sonography.

The present study used the deltoid muscle as a comparative component in the calculation of strain ratio. The deltoid appeared as a mixture of various colours in the elastogram. There were noted differences in stiffness within the muscle due to the different boundaries between the muscle fascicles, septa, fascia and vessels. The different vessels of arteries and veins deformed differently due to the elasticity strengths of the vessel walls. The veins showed soft (red) regions to correspond to their compressibility. The more tightly connected fascicles appeared blue/green as they were tightly packed. In the present study, the application of axial pressure with the transducer caused non-axial tissue displacement in parts of the tissue that were not tightly packed (like in softer tendons) and this caused the space at the calculated axial displacement to result

in a yellow-to-red (soft) line along that area. A similar effect was recorded in the studies by Drakonaki, Allen & Wilson, (2009) and Itoh *et al.* (2006). In the current study, the deltoid showed a composite of red at the deltoid-tendon interface, and a mesh of yellow-green with patches of scanty blue colour in keeping with higher strain as seen in soft tissue (Ophir *et al.*, 1991; Ophir *et al.*, 2000). These features were not discernible in the sonograms emphasizing the superiority of tissue imaging.

3.4.5 Strain ratio tool and size of the ROI window

The strain ratio tool mathematically compares the relative stiffness of two areas to further enhance diagnostic confidence, and it assigns numerical values to tissues as measures of quantification (Ohuegbe & Hussain, 2014). The current study showed a mean strain for normal supraspinatus tendons as 5.6 ($\pm 1.24SD$) with a slight difference in the mean strain ratio for males and females, the mean being slightly higher in males (5.7 $\pm 1.44SD$) than in females (5.4 $\pm 0.92SD$). There was statistically significant difference in the mean strain ratio values for males and females ($p = 0.02$). A pilot study that examined normal supraspinatus tendons in a smaller population of 25 adult volunteers of college students had similar findings with a mean strain ration of 4.5 for females and 5.6 for males (Hussain, 2008). In comparison, the current study evaluated a larger sample of 284 supraspinatus tendons. The result of the current study is more robust and generalizable. It is comparable to a study by Drakonaki, Allen & Wilson, (2009) on Achilles tendon that evaluated tendon-retroAchilles fat strain index in 50 subjects with a mean strain ratio of 1.06 - 2.39. In contrast, other studies by Klauser *et al.* (2006) and De Zordo *et al.* (2010) have been more of descriptive findings of the colour display in tendons with no evidence of quantitative evaluation. While no other study has undertaken a detailed assessment of normal and pathologic supraspinatus tendons using strain ratio, it made comparative critique of this research challenging as there were no similar studies to draw conclusions and comparisons from.

In line with above, the study by Waki, Murayama, Matsumura & Mitake (2007) showed that strain ratios were in accordance with elasticity ratios, while different objective data to estimate strain ratio were used. While the current study used

deltoid-to-tendon strain index to estimate strain ratio, the preliminary study by Hussain (2008) used a similar deltoid-to-tendon strain index. Further similar examples are seen in the work by Ueno *et al.* (2010) which used subcutaneous fat-to-lesion ratios while evaluating breast lesions. Zhi *et al.* (2008) used the breast glandular tissue at the same level as a reference point when conducting strain ratio measurements of breast lesions. Equally, Cho *et al.* (2010) used the adipose tissue for reference point at the same level in their study. In their study on Achilles tendon, Drakonaki, Allen & Wilson (2009) used deep lying fat and tendon to estimate strain ratio. A thorough reflection of the studies above indicate that strain ratio or index was used as a comparative index among different subjects rather than as an absolute strain measurement (Drakonaki, Allen & Wilson, 2009).

In a different study, Yerli, Yilmaz, Kaskati & Gulay (2011) posited that there could be a change in the strain index at different depths as superficial structures were more compressed than deeper structures. The study suggested that using the same depth in the reference point (ROI) could result in more accurate data (Yerli, Yilmaz, Kaskati & Gulay, 2011). The current study carefully attempted to maintain a representative uniform depth for the ROI in order to ensure a consistent and accurate data from the strain index. Therefore, the same technique was used to obtain the strain index in each shoulder to aid reproducibility. Consequently, the appearances of the sonoelastogram and strain indices obtained reflected the tissue elasticity of the examined region as was the case in the current study. In another vein, a study by Klauser, Faschingbauer & Jaschke (2010) on Achilles tendon recommended that the depth of the ROI should be three times the tendon size and width, and about three quarters of the screen for longitudinal scans. This is because a larger ROI that includes more neighbouring soft tissue makes a tendon show harder appearance with increased blue colour than a smaller ROI where less soft adjacent tissue is added. This can give erroneous results. Nonetheless, sonoelastography in its current status is considered a subjective technique. Both training and interpretive skills are required.

In contrast to above, a study by Yerli and colleagues suggested the use of normal tissue as the reference tissue at the same depth in order to obtain more

accurate data (Yerli, Yilmaz, Kaskati & Gulay, 2011). In a similar way, this opinion was supported by an unpublished case report of the Achilles tendon by Ohuegbe & Hussain (2014). The study compared Achilles tendon image findings in sonoelastography, and power Doppler. This report concluded that the relative comparison with the normal tendon area appears to give a better quantitative interpretation of the degree of tendon softening than comparing with fat. Another advantage of this pattern is that it showed the degree of softness of the degenerate area in comparison to the normal tendon area (Ohuegbe & Hussain, 2014). However, in organs where there is no normal tendon area to be used for comparison, this parameter is limited or cannot be applied.

In summary, the findings of this first phase of this study agree with similar studies reviewed in this thesis and others where lesion stiffness characterization was measured in kilopascals (Waki, Murayama, Matsumura & Mitake, 2007; Zhi *et al.*, 2008; Athanasiou *et al.*, 2010). The outcome will now be used as a reference standard for the next phase of this study which is presented in the following chapter.

Chapter 4 – Phase 2 Study

Verification of diagnostic characteristic tests for tendinopathy in patients with shoulder pain –“symptomatic” group

4.1 Introduction

This chapter presents the second phase of the study where symptomatic patients were examined. The study utilised a diagnostic research design. This phase investigated the presence or absence of supraspinatus tendinopathy in order to assess the accuracy of sonoelastography in diagnosing tendinopathy.

The study was based on three colour grading sonoelastographic patterns seen in tendons. Grade 1 pattern is the pattern for normal tendon and shows a characteristic blue-green pattern which is an indication of hard tissue appearance. Grade 2 pattern shows presence of yellow colouration within the tendon to indicate mild tendon softening. Grade 3 colour pattern shows evidence of red colouration within the tendon to indicate marked softening. The presence of grades 2 and 3 patterns are consistent with tissue softening or tendon pathology. The study measured the strain ratio of supraspinatus tendon and assessed the accuracy of sonoelastography when compared with ultrasound in the diagnosis of supraspinatus tendinopathy in patients with shoulder pain. The findings were compared with those obtained at clinical examination and strain ratio.

4.2 Methodology

In the verification for any diagnostic test, the selection of the gold standard is critical for accurate determination of true positive and true negative cases. Ultrasound is considered the gold standard for the diagnosis of tendinopathy (Khan *et al.*, 2003). However, it has been shown not to be a perfect gold standard because of its inability to measure tissue alterations in tendons (Waki, Murayama, Matsumura & Mitake, 2007; Zhi *et al.*, 2008; Athanasiou *et al.*, 2010). The differentiation of subtle tears and subclinical tendinopathy is a challenge to effective diagnosis with grey-scale ultrasound. In the light of this, clinical diagnosis was used as reference standard in most studies and in practice. This

was the case bearing in mind limitations associated with the morphology of the rotator cuff, the position and innervation of the subacromial bursa, and the lack of correlation between symptoms and contemporary methods of imaging (Lewis, 2009). However, the lack of specificity of the clinical tests for the rotator cuff has been demonstrated as a significant factor by Lewis & Tennent (2007) and Hegedus *et al.* (2008).

In view of the above, it was important to ensure the quality of this diagnostic research in order to avoid the risk of bias. The study used QUADAS 2 tool in the design of this research. The tool is useful in risk bias assessment and sources of variation in systemic reviews (Whiting, Rutjes, Reitsma, Bossuyt & Kleijnen, 2011). The following information was extracted for the design of this diagnostic accuracy study:

1. A reference standard (US / CD and SR) was used in the absence of a gold standard avoiding incorporation bias with the index tests (SE).
2. Bias in the selection of samples was circumvented as the study used consecutive non-probability sampling technique.
3. Work-up bias was avoided because the method of interpreting the reference standard was based on criteria (colour grading pattern and strain values) that were not subjective but based on the ECAM principle of sonoelastography. Therefore a second reader was not needed.
4. All the samples (patients) used in the study received both the same index and reference tests thereby avoiding verification bias.

Reference standards – the study compared the sensitivity, specificity, accuracy of sonoelastography against ultrasound, clinical diagnosis and strain ratio as reference standards.

Clinical diagnosis and ultrasound were used as the reference standards for diagnosis of supraspinatus tendinopathy. An additional new reference standard called strain ratio was also tested. Other studies have used more than one reference standard in their studies. These include the following: Abdel Razek & Ezzat (2008) used ultrasound and MRI as reference standards when evaluating

the accuracy, sensitivity and specificity of sonoelastography in supraspinatus tendons; De Zordo *et al.* (2009a) used ultrasound and clinical diagnosis as reference standard in sonoelastography of common extensor tendons; De Zordo *et al.* (2008) used ultrasound and clinical diagnosis as reference standard in sonoelastography of Achilles tendons; De Zordo *et al.* (2010) used ultrasound and clinical diagnosis as reference standard in sonoelastography of Achilles tendons.

These reference tests detected tendinopathy and avoided any incorporation bias with the index test (Levin *et al.*, 2005; Walz, Newman, Konin & Ross, 2010; De Zordo *et al.*, 2009a; De Zordo *et al.*, 2009b; du Toit *et al.*, 2008). The reference tests used are described below:

1. Clinical diagnosis: The patients were referrals from general practitioners, physiotherapists and chiropractors who had chronic shoulder pain (> 3 months) and clinically suspected to have supraspinatus tendinopathy. The patients complained of persistent chronic pain and pain during rest and at rest with a mean duration of 11.4 months (range 3-38 months). Clinical examination of these patients was performed by a Chiropractor with 20 years' experience. The examination included assessment for pain arising from movement, tenderness and the 'painful arc' sign. Clinical assessment was performed to evaluate the presence of focal and generalized symptoms and manifestations of supraspinatus tendinopathy using the above stated clinical test that suggests its presence (Jobe & Jobe, 1983; Lewis, 2009; Neer, 1983; Hawkins & Kennedy, 1980; Zaslav, 2001).

2. In order to use the strain ratio as reference standard, a ROC curve analysis was constructed. An optimum cut-off strain ratio value was used to distinguish elastography in patients with (positive) or without (negative) tendinopathy. The cut-off indicated an optimal strain index criterion which was used to differentiate between normal and abnormal (tendinopathic) tendons, and obtained the best cut-off point for achieving maximum sensitivity and specificity. It evaluated the accuracy or diagnostic performance of sonoelastography to differentiate tendinopathy from normal cases using the area under the ROC curve (AUC). The optimum cut-off strain ratio value used for the study was 4.0. The ROC

curve is a good measure of test accuracy as it does not depend on the prevalence of disease or the cut points used to form the curve.

To plot the ROC curve, from the values of specificity, false positive rate (FPR) represented as $1 - \text{specificity}$ was calculated. The test sensitivity was plotted as the y-coordinate versus the FPR as the x-coordinate to produce the ROC curve. The detail of this ROC curve is shown in Figure 4.13 and Section 4.3.8.1.

QUADAS 2 was used to ascertain the quality issues in methodology while STARD (Standard for the Reporting of Diagnostic Accuracy Studies) is similar but assesses the quality of reporting of studies by stressing on its accuracy and completeness at the end of the study (Oliveira, Gomes & Toscano, 2011). A flow chart is shown outlining the composition of the study and pathway of investigation beginning with sample selection to the results in keeping with STARD to certify accurate and full reporting of this study (Figure 4.1).

STUDY FLOW CHART

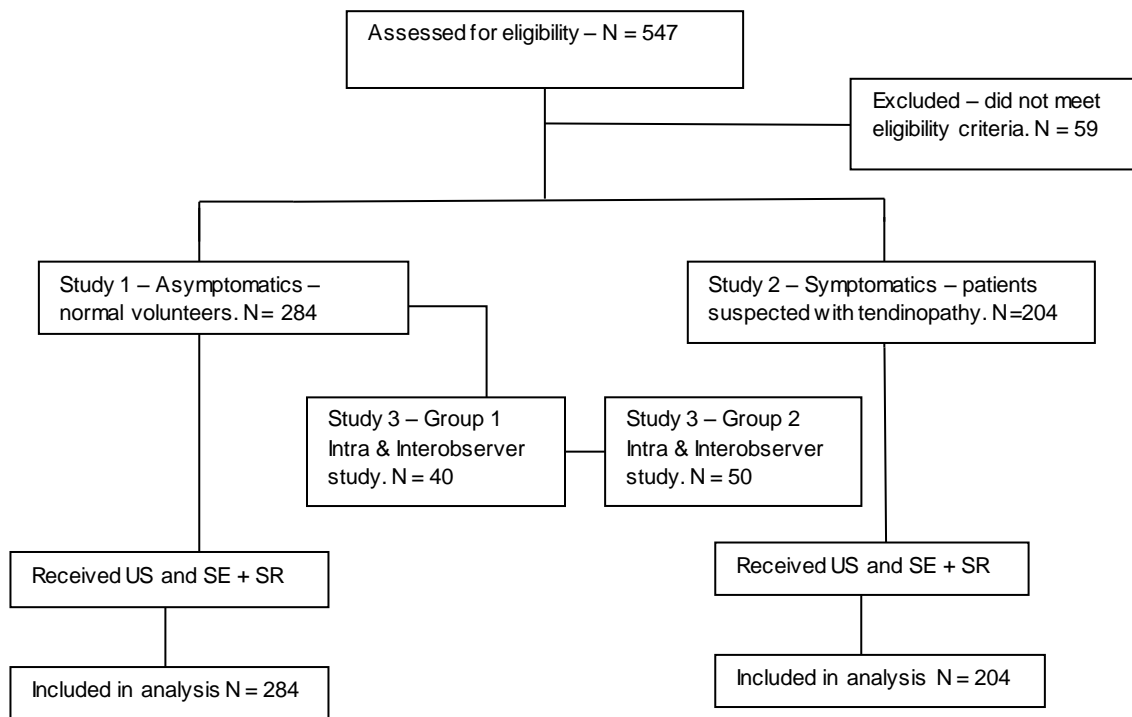


Figure 4.1: Flow chart showing composition of study.

Figure 4.1 showed that 547 participants were approached and 488 agreed to enrol in the study while 59 were excluded who did not meet the eligibility criteria. From the 488, a total of 284 represented the asymptomatic group and 204 represented the symptomatic group.

The format of reporting this study is in line with the recommended STARD format which includes: introduction, method, result and discussion. This format introduces accuracy, clarity and completeness of the information used in the reporting of studies (Bossuyt *et al.*, 2003; Standards for the Reporting of Diagnostic accuracy studies (STARD) Statement, 2008).

Recruitment of patients into the stage two of the study started in April 2011 and data collection was completed in August 2012. The patients were referrals from general practitioners, physiotherapists, chiropractors' referrals who had shoulder pain with indications on the request forms clearly stating that the patient had been evaluated and was positive for Jobe's test, Neer's sign, Hawkin's or IRRS tests for tendinopathy, and ultrasound was considered the first line imaging investigation of choice. Their participation was entirely voluntary and anyone was free to withdraw from the study if they wanted at any point.

Information sheets and consent forms were used to inform and gain consent of patients' participation (see Appendices D, E and F). Inclusion and exclusion criteria (section 3.7.4) were necessary in order to have a patient sample size that would give results that are reproducible and eliminate all biases that affect the validity of the study. Standard demographic data (sex, age) were obtained at the time of inclusion.

The measurements made included grey-scale grades (1, 2 and 3) for ultrasound and colour grades (1, 2 and 3) for sonoelastography and strain ratio values.

The participants for this research were selected in line with the principles and criteria for diagnostic testing. They were selected on their suspicion of having a particular disease. There was no confirmation of the presence or absence of that disease. This method of selection was undertaken as patients were scanned and examined at the research centre where this study was undertaken (CUS, AECC Bournemouth). Patients suspected of having the disease (tendinopathy) due to

their presenting signs and symptoms (Moons, Biesheuvel & Grobbee, 2004) were recruited. This system of registering subjects on their clinical presentation rather than on the presence or absence of that disease improved the validity and clinical relevance of diagnostic accuracy research (Moons, Biesheuvel & Grobbee, 2004).

4.2.1 Sample selection and data collection

Purposive method of data collection was used to collect data in a cohort of patients with clinically diagnosed supraspinatus tendinopathy (symptomatic group) according to the Standards for Reporting of Diagnostic Accuracy (Bossuyt *et al.*, 2003).

4.2.2 Subject selection criteria

Inclusion criteria for patients

- Aged between 18 years and above.
- Currently taking part in sports >1x/week (or would be if not for supraspinatus tendon symptoms).
- The patients were referrals from general practitioners, physiotherapists and chiropractors who had chronic shoulder pain (> 3 months) and clinically suspected to have supraspinatus tendinopathy.
- The patients complained of persistent chronic pain and pain during rest and at rest with a mean duration of 11.4 months (range 3-38 months).
- Ability to provide own informed consent.
- Good understanding of English language/English language as a first language.

Exclusion criteria

- Patients ≤ 17 years and > 90 years.
- Shoulder injections in the previous six months.
- Rotator cuff surgery.

4.2.3 Sample size calculation

Sample Size estimation for Phase 2

The number of subjects used for this study depended on three quantities that were pre-specified by the researcher:

- 1) the width of a CI (clinically acceptable precision);
- 2) the prevalence of the condition or disease in the population of interest, and;
- 3) hypothesized values of sensitivity and specificity.

Step 1

Previous research in supraspinatus tendinopathy using ultrasound and MRI showed very high sensitivity and specificity. To be conservative, this research hypothesizes that the values in the shoulder will be lower.

The selected sensitivity (SN) and specificity (SP) are

SN = 0.80 and SP = 0.85.

A clinically acceptable width of the 95% CIs for sensitivity and specificity was chosen to be no larger than 10%; i.e., a SN from 0.70 to 0.80 and a SP from 0.75 to 0.95. Set $W = 0.10$.

In the AECC, 30% of the ultrasound shoulder pathologies (upper range of prevalence) were positive for tendinopathy, i.e., set $P = 0.30$.

To calculate the need for adequate *sensitivity*, this formula is used (Buderer, 1996; Batavia 200; Bachmann, ter Riet, Weber & Kessels, 2009):

- $TP + FN = Z^2 \times (SN (1 - SN) / W^2)$
- $N(sn) = TP + FN / P$

($Z = 1.96$; TP = true positive; FN = false negative)

Step 2

$$TP + FH = 1.96^2 \times 0.8 \times (1 - 0.8) / 0.10^2 = 61.44$$

Step 3

$$N(sn) = TP + FN / P$$

$$N1 = 61.44 / 0.30 = 204$$

To calculate the need for adequate *specificity*, this formula is used:

- $FP + TN = Z^2 \times (SP (1 - SP)) / W^2$
- $N(sp) = FP + TN / (1 - P)$

(FP = false positive; TN = true negative)

Step 4

$$FP + TN = 1.96^2 \times 0.85 \times (1 - 0.85) / 0.10^2 = 48.98$$

Step 5

$$N(sp) = FP + TN / (1 - P)$$

$$N2 = 48.9804 / (1 - 0.30) = 69.972$$

Step 6

$N1 > N2$, thus N , rounded to the next higher whole number, is 204 subjects.

The 204 supraspinatus tendon (N subjects) were recruited for the study (out of 263 as 59 were dropped who did not meet the eligibility criteria – see Figure 4.1) with the assumption that the prevalence of disease in the sample was likely to reflect the prevalence found in the target population. This method allowed for the control of the CIs for both sensitivity and specificity (Buderer, 1996; Batavia 2001; Bachmann, ter Riet, Weber & Kessels, 2009). Sample size calculation may be of little value in early exploratory studies where scarce data are available on which to base the calculations, though this may be addressed by performing a pilot study first and using the data from that (Jones, Carley & Harrison, 2003). This study was based on a pilot study (Hussain, 2008) presented at the 40th BMUS conference which used a sample size of 25.

4.2.4 Diagnostic technique

The examination protocol used in this study was similar to that used in Study 1 (Sections 3.2.5 and 3.2.6). The same ultrasound machine: (Hitachi Medical EUB 7500, EUP – L54M, 6-13 MHz probe) and technique were also used. Each supraspinatus tendon of every referred patient was examined longitudinally using both sonoelastographic examination and grey-scale ultrasound. Sonoelastographic data demonstrating longitudinal images of the supraspinatus tendon with colour grading and strain ratio information were collected and stored electronically in the ultrasound cine-memory for analysis. This electronic storage allowed them to be coded and anonymised before being stored to prevent any patient's identity being revealed.

The patients were scanned with grey-scale ultrasound by another musculoskeletal (MSK) sonographer with more than 5 years' experience in MSK ultrasound who had no clinical knowledge of the patient's clinical history. The patients were scanned and assessed with SE and SR measurements by the principal author who was not blinded to the clinical history of the patients. The time interval between the GSU and the SE / SR scans was 30 minutes.

4.2.5 Statistical tests and method of analysis

(a) Visual inspection of the supraspinatus tendon to determine ultrasound and

sonoelastography patterns:

The ultrasound patterns were evaluated using Archambault *et al.* (1998) grading system and the sonoelastography appearances were evaluated using an experimentally proven colour grading system (Frey, 2003) as previously discussed in section 3.2.8 of Phase 1 study.

Grade 1: normal-appearing tendon (smooth margins, homogeneous echotexture);

Grade 2: enlarged tendon (homogeneous echotexture, hypoechogenicity);

Grade 3: hypoechoic area with/without tendon enlargement, or with calcification.

Grade 1 tendons represent normal tendon, and Grades 2 and 3 tendons represent abnormal or pathologic tendon.

The sonoelastography appearances were evaluated using an experimentally proven colour grading system (Frey, 2003).

Grade 1: if the tendon was blue/green (hard tissue);

Grade 2: yellow colour evident within the tendon (intermediate tissue or mild softening);

Grade 3: red colour evident within the tendon (soft tissue).

(b) Descriptive statistics were used to characterize the study population. Normally distributed data were described with the mean and standard deviation. Proportions were also compared with the chi-square test to find out if there was a significant agreement between ultrasound and sonoelastography in categorizing patients.

Diagnostic accuracy, sensitivity, specificity, and positive and negative predictive values, and positive and negative likelihood ratios were calculated for ultrasound and sonoelastography using both clinical diagnosis and strain ratio index as reference standards (Moons, Biesheuvel & Grobbee, 2004).

To find out if there is a significant difference between male and female groups, an independent-samples *t-test* was conducted to compare the strain ratio values of males and females. A $p \leq 0.05$ was considered to indicate statistical significance (i.e., differences were considered significant at the 5% level if the p values were ≤ 0.05). All statistical parameters were calculated using the

Statistical Package for the Social Sciences (SPSS 20.0 for Windows, Chicago, IL, USA).

The *kappa* agreement between the tests (ultrasound and sonoelastography) was evaluated in the positive and negative groups to assess the strength of agreement according to Landis and Koch (1977). A *kappa* value of 0.00–0.20 indicates poor agreement, a *kappa* value of 0.21–0.40 indicates fair agreement, a *kappa* value of 0.41–0.60 indicates moderate agreement, a *kappa* value of 0.61–0.80 indicates good agreement, and a *kappa* value of 0.81–1.00 indicates very good agreement.

To find out whether there is a significant statistical difference between symptomatic and asymptomatic groups, an independent samples *t*-test was conducted to compare the strain ratio values of both groups.

The inter-rater agreement assessing the consistency of the diagnostic accuracy of two different diagnostic tests (ultrasound and strain ratio, and sonoelastography and strain ratio) was evaluated. The *kappa* measure of agreement value with a significance of $p < 0.0005$ was considered according to Peat (2001). A value of 0.5 = moderate agreement; value of > 0.7 = good agreement; value of > 0.8 = very good agreement.

Age matching of healthy volunteers to patients was not possible ($p < 0.001$) because the healthy volunteer sample was from a younger population than the patient sample. The mean strain indices of all patients were calculated including the mean strain values for positive and negative symptomatics.

Sensitivity measured the proportion of actual positives which were correctly identified as such (e.g. the percentage of patients with shoulder pain who are correctly identified as having tendinopathy). Specificity measured the proportion of negatives which were correctly identified (e.g. the percentage of patients who are correctly identified as not having tendinopathy). Accuracy represented the proportion of true results (both true positives and true negatives) in the population.

The positive predictive value (PPV) is the proportion of subjects with positive test results who were correctly diagnosed. It is a critical measure of the performance

of a diagnostic method as it reflects the probability that a positive test reflects the underlying condition being tested for. The negative predictive value (NPV) is the proportion of subjects with a negative test result who were correctly diagnosed. A high NPV means that when the test yields a negative result, it is most likely correct in its assessment.

Calculation of confidence interval - a CI is a particular kind of interval estimate of a population parameter which is used to indicate the reliability of an estimate. It is an observed interval (i.e. it is calculated from the observations), in principle different from sample to sample, that frequently includes the parameter of interest, if the experiment is repeated.

In conclusion, this study used a primary method of data collection for the research while carefully taking all the appropriate ethical considerations and steps. Proper statistical designs were adopted with the right statistical method of analysis to ensure the data were subjected to the appropriate statistical scrutiny and analysis. This was to ensure all the objectives of this research were achieved while answering correctly all the research questions.

4.3 Results

This section states the results of all the of the second population group regarded as the symptomatics. The factors evaluated in this group included the following:

- appearances of abnormal ultrasound and sonoelastography patterns of supraspinatus tendons,
- the strain ratio values of the abnormal tendons and the establishment of strain ratio cut-off value using ROC curve
- the comparison of the diagnostic accuracy of ultrasound and sonoelastography using two different reference standards (clinical diagnosis and strain ratio) in order to establish which was more consistent in providing accurate results.

4.3.1 Demographic data and standard descriptive statistics of ultrasound pattern

Using Archambault *et al.* (1998) grading system as discussed in Stage 1 result, a total of 204 tendons were evaluated.

Table 4.1: Ultrasound grade versus gender distribution.

Grade		Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F	
Ultrasound	1	91 (44.6%)	73 (35.8%)	164 (80.4%)
	2	19 (9.3%)	21 (10.3%)	40 (19.6%)
	3	0	0	0
Total		110 (53.9%)	94 (46.1%)	204 (100%)

The ultrasound pattern of the tendons was easily visible. The tendons showed a characteristic homogeneous, mid-grey echotexture with normal fibrillar echopattern with no evidence of obvious hypoechoic areas or calcifications in 164 (80.4%) tendons as shown in Table 4.1. This pattern corresponded to Grade 1 grading pattern indicating hard tissue appearance.

A total of 40 (19.6%) tendons showed evidence of hypoechoic areas within the tendons in keeping with Grade 2 grading pattern. The hypoechoic areas appeared either focal or relatively diffuse. The results also showed that a total of 110 (53.9%) male tendons and 94 (46.1%) female tendons demonstrated Grade 1 colour pattern. Grade 2 colour pattern was demonstrated in 19 (9.3%) male tendons and 21 (10.3%) female tendons.

4.3.2 Demographic data and standard descriptive statistics of sonoelastography pattern

The symptomatic group represented the cohort of patients with clinically diagnosed tendinopathy which provided the data for the Phase 2 of the research. The data were used to compare with the normal strain ratio values of the

asymptomatic group in Phase 1 of this research. The results of this phase presented strain ratio indices of positive asymptomatic participants that were used to produce a cut-off point that acted as a reference standard to compare the diagnostic accuracy of ultrasound and sonoelastography in the assessment of tendinopathy in the participants.

A total of 204 shoulders were evaluated and each supraspinatus tendon was imaged using ultrasound and sonoelastography, and the strain ratio indices of each sonoelastography were measured. There were 110 males (53.9%) and 94 females (46.1%) in the sample giving a total of 204 participants. The range of age was from 20 to 90 years with a mean of 38.6 and a standard deviation of ± 14.7 years.

Table 4.2: Sonoelastography grade versus gender distribution.

Grade		Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F	
Sonoelastography	1	65 (31.9%)	43 (21.1%)	108 (52.9%)
	2	25 (12.2%)	26 (12.7%)	51 (25.0%)
	3	20 (9.8%)	25 (12.2%)	45 (22.1%)
Total		110 (53.9%)	94 (46.1%)	204 (100%)

In Table 4.2, a total of 108(52.9%) of supraspinatus tendon showed Grade 1 colour grade, 51 (25%) demonstrated Grade 2 and Grade 3 was seen in 45(22.1%) tendons (Table 4.2). The tendon elastographic pattern was very easily visible. The tendons showed a characteristic blue-green pattern predominantly. This was evident in 108 (52.9%) tendons. This pattern corresponded to Grade 1 colour pattern. This indicated hard tissue or normal appearance of the supraspinatus tendon. The combination of blue and green colours within the tendon varied as this represents the degree of tissue compressibility.

A total of 51 (25%) tendons showed evidence of yellow colouration within the tendons in keeping with Grade 2 colour grading pattern. This is an indication of intermediate tissue thickness. A total of 45 (22.1%) tendons demonstrated evidence of red colouration in keeping with soft tissue pattern. Grades 2 and 3 colour patterns indicate abnormal tendon appearance.

A total of 65 (31.9%) males and 43 (21.1%) females showed Grade 1 colour grade (Figure 4.2).

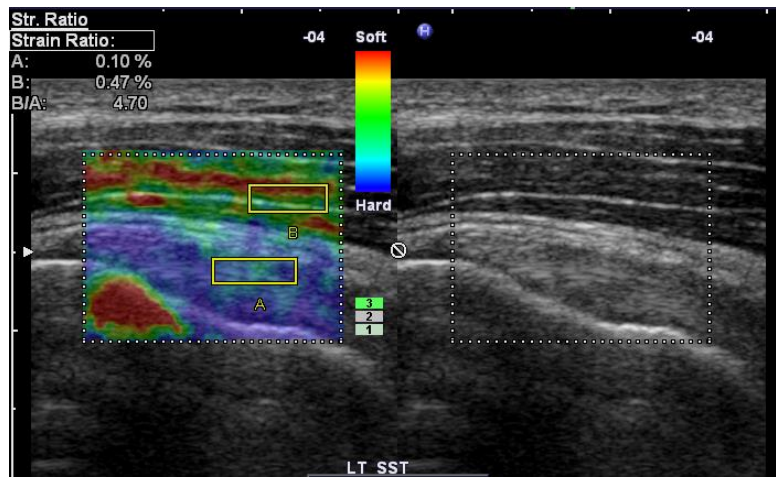


Figure 4.2: An elastogram of a Grade 1 supraspinatus tendon of a 26year old male.

In Figure 4.2, the longitudinal sonogram and elastogram of the left supraspinatus tendon show a uniform, mid-grey echotexture with normal fibrillar echopattern and blue-green colour codes in keeping with a hard structure appearance and grade 1 colour grading pattern.

Grade 2 colour grade pattern as shown in Figure 4.3 was demonstrated in 25 (12.2%) males and 26 (12.7%) females. Grade 3 colour grade pattern was seen in 20 (9.8%) males and 25 (12.2%) males (Figures 4.3). These figures and percentages are further shown in bar charts in Figure 4.4 and Figure 4.5.

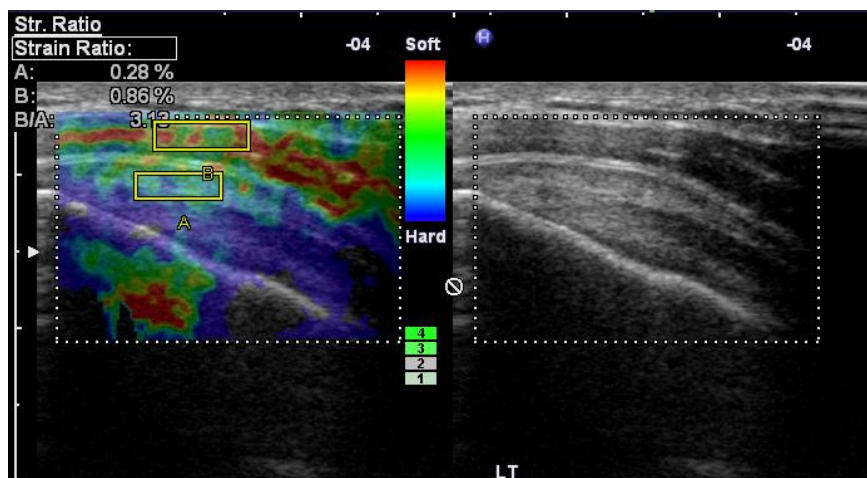


Figure 4.3: An elastogram of a Grade 2 supraspinatus tendon of a 39 year old female.

In Figure 4.3 the longitudinal sonogram of the left supraspinatus tendon on the right of the image shows a uniform, mid-grey echotexture with normal fibrillar echopattern suggesting a hard structure appearance. The elastogram on the left of image shows patches of yellow and green in anterior bursal part of the tendon consistent with tissue softening. The strain ratio of 3.13 indicates soft tendon appearance in this area.

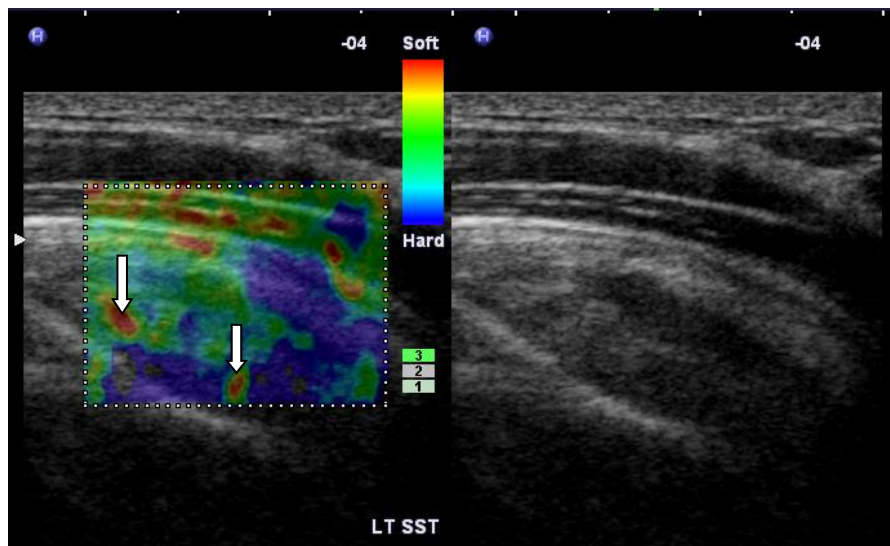


Figure 4.4: An elastogram of a Grade 3 supraspinatus tendon of a 52 year old male.

The longitudinal sonogram of the left supraspinatus tendon on the right of the image in Figure 4.4 shows a thickened tendon with a heterogeneous fibrillar echopattern suggesting tendinopathy. The elastogram on the left of image shows patches of yellow and red (white arrows) within the tendon in keeping with tissue softening consistent with tendinopathy.

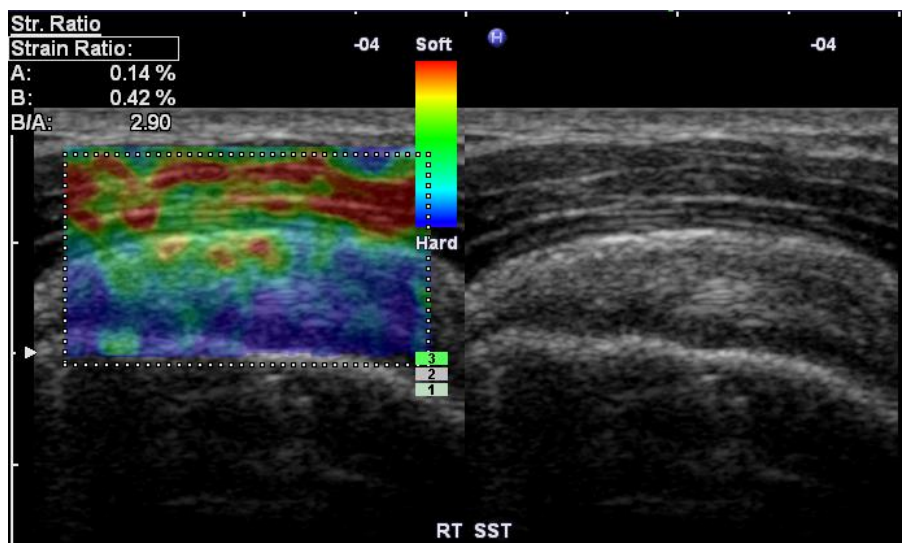


Figure 4.5: An elastogram of a Grade 3 supraspinatus tendon of a 42 year old male.

Figure 4.5 shows patches of red and yellow colours in the sonoelastogram which indicate tendinopathy on the right of the image of the left supraspinatus tendon. The strain ratio is low with a value of 2.90. The sonogram on the right of the image does not clearly demonstrate these soft areas as areas of patchy hypoechogenicity.

The distributions of these percentages as shown in Table 4.2 are shown in 2-dimensional bar charts in Figure 4.6 and Figure 4.7. The bar chart of Figure 4.5 shows the overall percentages of sonoelastography grades 1, 2, 3 and their total in all the males, females and both genders combined.

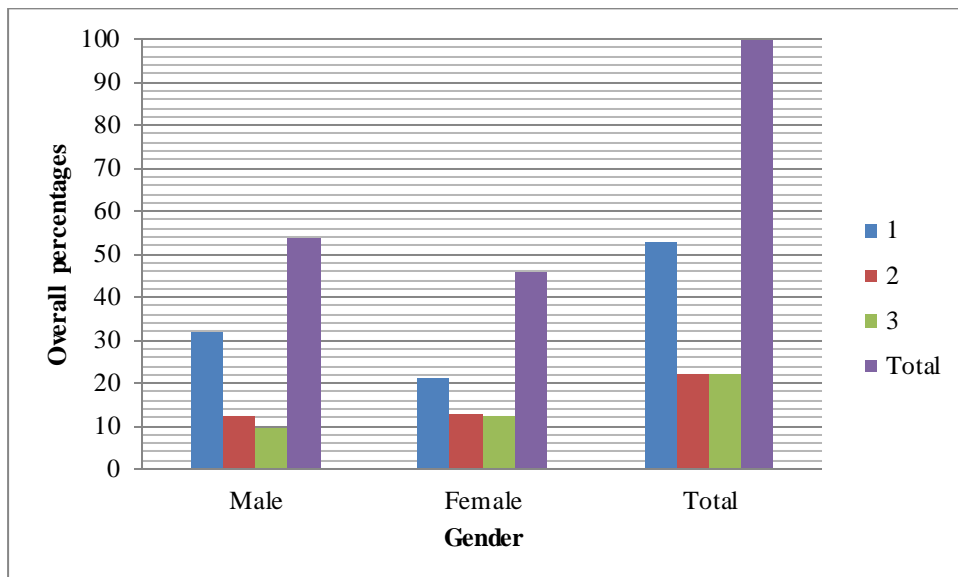


Figure 4.6: Distribution of sonoelastography colour grade percentages in males, females and both.

Bar chart of overall sonoelastography colour grade percentages and gender showing the distribution of the sonoelastography colour grade percentages in males, females and both (1 - sonoelastography grade 1; 2 - sonoelastography grade 2; 3 - sonoelastography grade 3).

The bar chart of Figure 4.7 shows the overall percentages of all the males, females and both genders combined in sonoelastography grades 1, 2, 3 and their total.

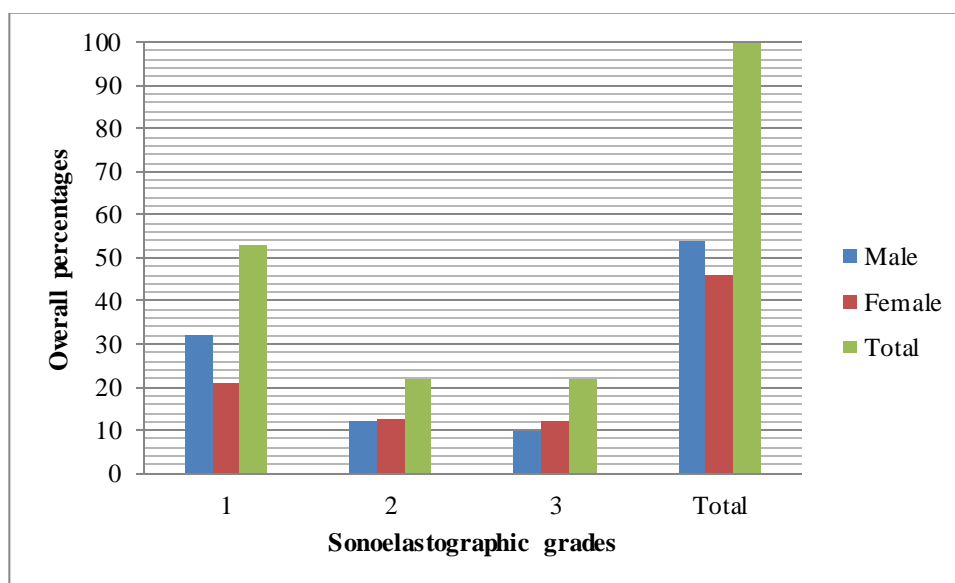


Figure 4.7: Distribution of the percentages of males, females and combined sonoelastography grades.

Bar chart of overall gender percentages and sonoelastography colour grades showing the distribution of the percentages of males, females and combined sonoelastography grades (1-sonoelastography grade 1; 2-sonoelastography grade 2; 3-sonoelastography grade 3).

4.3.3 Modified grading pattern

Table 4.3: Sonoelastography grades versus gender distribution (modified).

		Gender <i>n</i> (%)		Total <i>n</i> (%)
		M	F	
Sonoelastography	1	65 (31.9%)	43 (21.1%)	108 (52.9%)
	2	45 (22.0%)	51 (24.9%)	96 (47.1%)
Total <i>n</i> (%)		110 (53.9%)	94 (46.1%)	204 (100%)

Grade 1 or 'hard tissue' signifies normal tendon, and Grade 2 and Grade 3 or 'soft tissue' signifies abnormal or pathologic tendon. For the purpose of statistical analysis, Grade 2 and Grade 3 were assigned 'Grade 2' as both indicated the presence of pathology. This therefore gave a total of 108 (52.9%) presenting with Grade 1 colour pattern, and 96 (47.1%) presenting with Grade 2 colour pattern. Sixty five (31.9%) males and 43 (21.1%) females showed Grade 1 colour pattern, and 45 (22.0%) males and 51(24.9%) females showed Grade 2 colour pattern. These are shown in Table 4.3 and bar chart in Figure 4.7.

The bar chart of Figure 4.8 shows the overall percentages of all the males, females and both genders combined in sonoelastography grades 1, 2, 3 and their total.

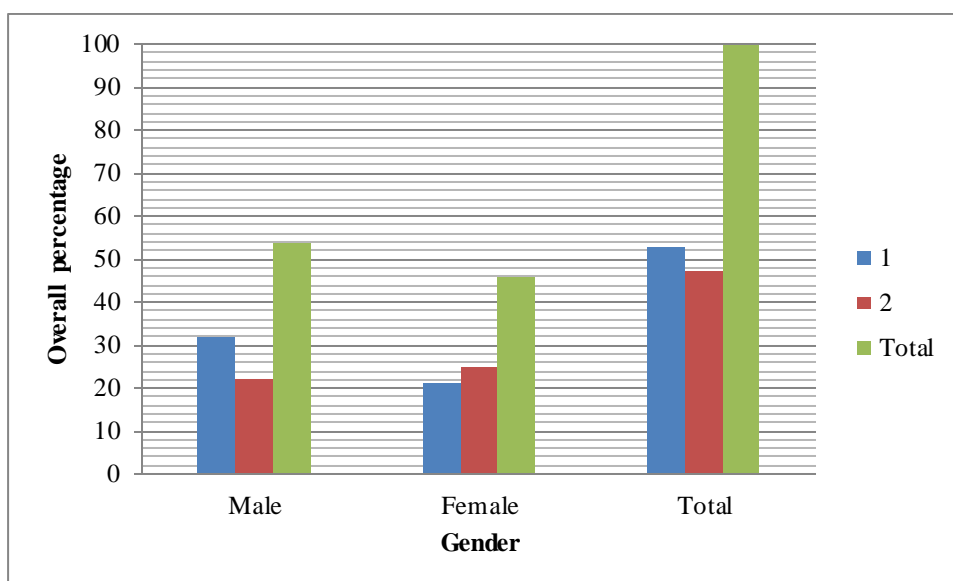


Figure 4. 8: Distribution of the percentages of males, females and combines sonoelastography grades.
 Bar chart of overall gender percentages and sonoelastography grades showing the distribution of the percentages of males, females and combined sonoelastography grades (1- sonoelastography grade 1; 2 - sonoelastography grade 2).

The bar chart of Figure 4.9 shows the overall percentages of sonoelastography grades 1, 2, 3 and their total in all the males, females and both genders combined.

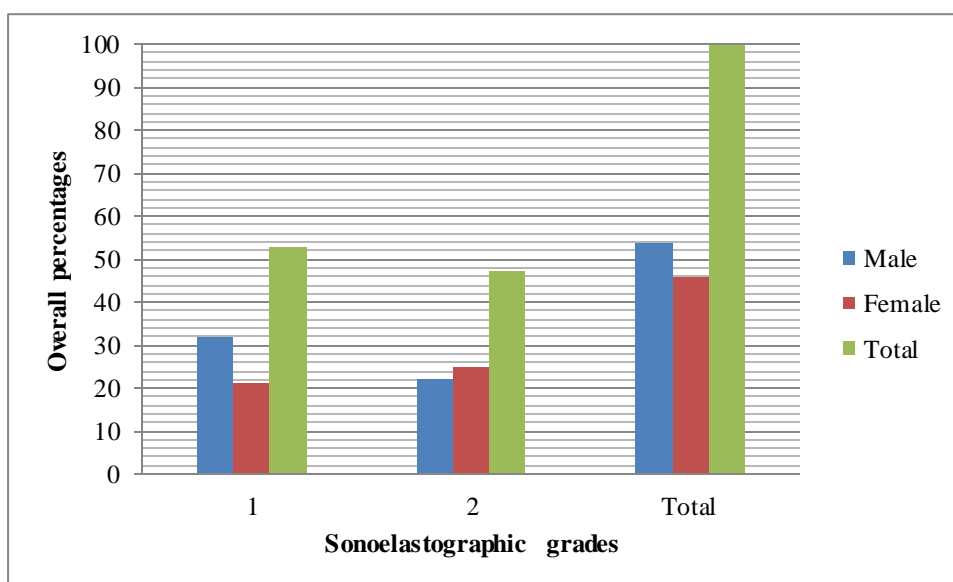


Figure 4.9: Distribution of the sonoelastography colour grade percentages in males, females and both.
 Bar chart of overall sonoelastography grade percentages and gender showing the distribution of the sonoelastography colour grade percentages in males, females and combined sonoelastography grades (1- sonoelastography grade 1; 2 - sonoelastography grade 2).

4.3.4 Comparison of the diagnostic accuracy of ultrasound and sonoelastography in detecting tendinopathy in the supraspinatus tendon

Two reference standards were used in comparing the accuracy of detection of tendinopathy in the supraspinatus tendons. The two reference standards used were

1. Clinical diagnosis
2. Strain ratio.

4.3.4.1 Diagnostic accuracy of ultrasound and sonoelastography using clinical diagnosis as reference standard

Clinical diagnosis was used as a reference standard to determine the accuracy of US in the diagnosis of supraspinatus tendinopathy.

Table 4.4: Diagnostic properties of individual test using Clinical diagnosis as a reference test against Ultrasound.

		Clinical diagnosis	
		Positive	Negative
Ultrasound	Positive	26 (12.7%)	70 (34.3%)
	Negative	14 (6.9%)	94 (46.1%)

The figures in Table 4.4 represent positive and negative results of the test (ultrasound) in the symptomatic group.

From the quantitatatives derived from a 2x2 contingency table, the accuracy of ultrasound was 59% with a sensitivity (65%) and specificity (57%) as shown in Table 4.5. The positive and negative predictive values were 27% and 87% respectively.

Table 4.5: Details of 2x2 contingency table results for diagnostic accuracy of Ultrasound using Clinical diagnosis as reference standard.

Variables	Values (95% Confidence intervals)	Comments
Accuracy	59% (53-64%)	This is the proportion of patients correctly classified by US
Sensitivity	65% (50-78%)	This is the proportion of patients with tendinopathy who have a positive test result
Specificity	57% (54-61%)	This is the proportion of patients without tendinopathy who have a negative test result
Positive Predictive Value (PPV)	27% (21-33%)	This value is the proportion of patients with a positive test result for tendinopathy who actually have tendinopathy.
Negative Predictive Value (NPV)	87% (81-92%)	This value is the proportion of patients with a negative test result for tendinopathy who do not have tendinopathy.
Positive Likelihood Ratio	1.5 (1.1-2.0)	This shows that a patient with tendinopathy is 1.5 times more likely to get a positive result than a person without tendinopathy.
Negative Likelihood Ratio	0.6 (0.4-0.9)	This shows that a patient with tendinopathy is 0.6 times less likely to get a negative result than a person without tendinopathy.

Table 4.6: Diagnostic properties of individual tests using Clinical diagnosis as a reference test against Sonoelastography.

		Clinical diagnosis	
		Positive	Negative
Sonoelastography	Positive	30 (14.7%)	61 (29.9%)
	Negative	10 (4.9%)	103 (50.5%)

The figures in Table 4.6 represent positive and negative results of the test (sonoelastography) in the symptomatic group.

From the quantitatIVES derived from a 2x2 contingency table, the accuracy of sonoelastography was 65% with a sensitivity (75%) and specificity (63%) as shown in Table 4.7. The positive and negative predictive values were 33% and 91% respectively.

Table 4.7: Details of 2x2 contingency table measures of diagnostic accuracy for Sonoelastography using Clinical diagnosis as reference standard.

Variables	Values (95% Confidence intervals)	Comments
Accuracy	65% (59-70%)	This is the proportion of patients correctly classified by US.
Sensitivity	75% (60-86%)	This is the proportion of patients with tendinopathy who have a positive test result.
Specificity	63% (59-66%)	This is the proportion of patients without tendinopathy who have a negative test result.
Positive Predictive Value (PPV)	33% (26-38%)	This value is the proportion of patients with a positive test result for tendinopathy who actually have tendinopathy.
Negative Predictive Value (NPV)	91% (86-95%)	This value is the proportion of patients with a negative test result for tendinopathy who do not have tendinopathy.
Positive Likelihood Ratio	2.0 (1.5-2.5)	This shows that a patient with tendinopathy is 2.0 times more likely to get a positive result than a person without tendinopathy.
Negative Likelihood Ratio	0.4 (0.2-0.7)	This shows that a patient with tendinopathy is 0.4 times less likely to get a negative result than a person without tendinopathy.

***Kappa* measure of agreement between tests**

The *kappa* agreement between the tests (ultrasound and sonoelastography) is evaluated in the positive and negative groups. In the positive group, the *kappa* value is 0.35, and this showed a fair strength of agreement (Landis and Koch, 1977).

In all patients (positive + negative), agreement between sonoelastography and ultrasound produced a *kappa* value of 0.27 and this also showed that the strength of agreement was fair.

Table 4.8: Table for *Kappa* values and strength of agreement (Landis and Koch, 1977).

Strength of Agreement	Poor	Fair	Moderate	Good	Very Good
<i>Kappa</i> (k)	<0.20	0.21-0.40	0.41-0.60	0.61-0.80	0.81-1.00

4.3.4.2 Diagnostic accuracy of ultrasound and sonoelastography using strain ratio as reference standard

Before ascertaining the diagnostic accuracy of ultrasound and sonoelastography using strain ratio as reference standard, it is important to consider the results of strain ratio in the positive symptomatic group. This is important as it will be referred to later when the estimated cut-off value for the reference standard is determined.

4.3.5 Results of strain ratio in positive and negative symptomatic group

The mean strain ratio value in the positive symptomatic group was 3.59 ($n = 96$) with a standard deviation of ± 5.16 . There were outliers between 10.1 and 52.2 in cases of calcific tendinopathy as seen in the histogram in Figure 4.10 (see also Figure 4.11).

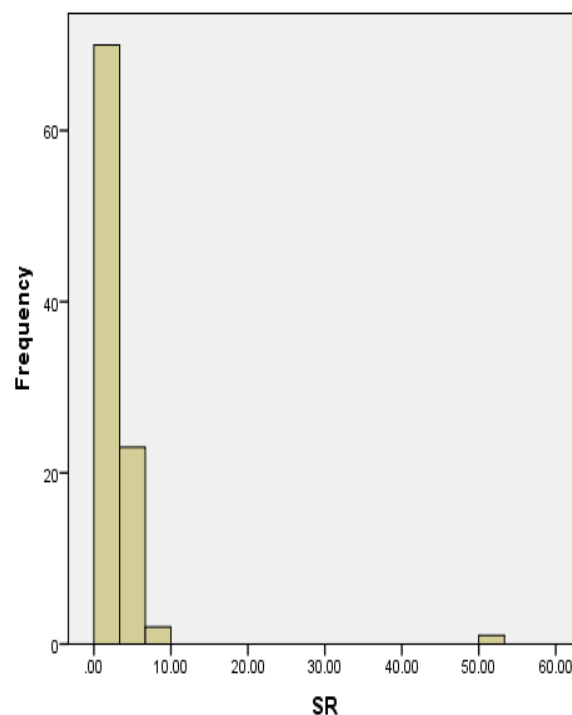


Figure 4.10: Histogram of mean strain frequency in the positive symptomatic group.

The mean strain ratio value in the negative symptomatic group was 6.35 ($n = 108$) with a standard deviation of ± 2.52 . There were outliers between 10.1 and 26.2 in cases of calcific tendinopathy as seen in the histogram in Figure 4.11.

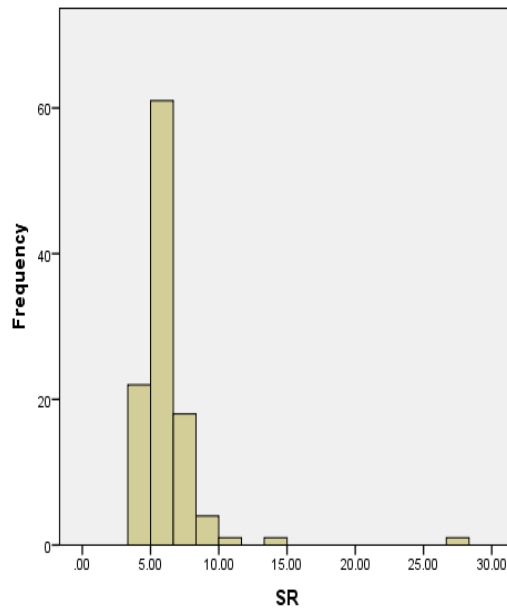


Figure 4.11: Histogram of mean strain frequency in the negative symptomatic group.

4.3.6 Results of strain ratio in combined positive and negative symptomatic group

The mean strain ratio value in the symptomatic group was 5.05 with a standard deviation of ± 4.21 in a total of 204 tendons including all the outliers as shown in the histogram in Figure 4.12.

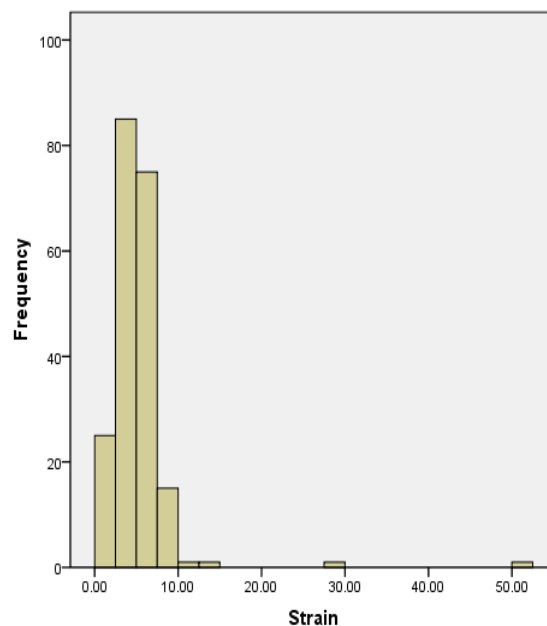


Figure 4.12: Histogram of mean strain frequency in the whole symptomatic group.

The overall mean of sonoelastographic strain indices (N = 204; mean = 5.05; test of normality using Kolmogorov-Smirnov statistic of 0.000) ensures no violation of the assumption of normality. From the box-plot (Figure 4.13), the rectangle indicates that the 50% of values lay around 5.0 strain values, and this in essence compares with the mean value seen in the histogram in Figure 4.12.

Also the box plot whiskers show the smallest (0.9) and largest (9.4) values. There were noted outlier (small circle) and extreme values (asterisks) in the box-plot in keeping with tendons with high strain values consistent with high calcium content or calcific tendinopathy.

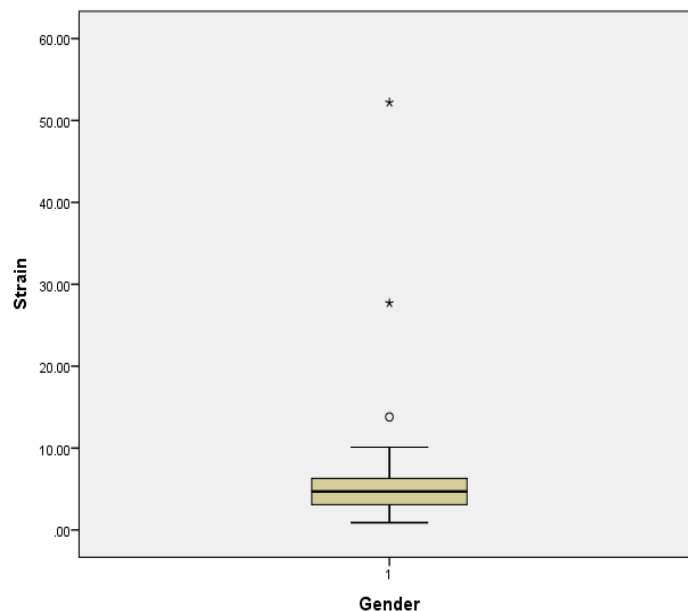


Figure 4.13: Distribution of the overall mean of sonoelastographic strain indices in the symptomatic group (Gender refers to all males and females).

These high strain values also possibly indicated the strength or consistency of calcium within the tendon. This could also suggest how soft the calcium would be in aiding any intervention to rid the tendon of calcium (e.g., ultrasound-guided barbotage).

4.3.7 Mean strain ratio of all sonoelastography grades versus gender

The mean strain values of the sonoelastography grades were seen to be different in each grade in males and females as shown in Figure 4.14. The mean

strain values of both male and female showed that grade 1 colour demonstrated higher mean strain values in both expectedly as these were within normal range. The mean was higher in males than females in grade1. In grade 2, the mean strain value was lower in males than females.

To find out whether there is a significant difference between male and female groups, an independent-samples *t*-test was conducted to compare the strain ratio values of males and females (Pallant, 2007). There was no significant difference in values for males ($M = 1.41$, $SD = 0.49$) and females ($M = 1.54$, $SD = 0.50$); $t(202) = 1.91$, $p = 0.06$ (two-tailed) as the value is above 0.05.

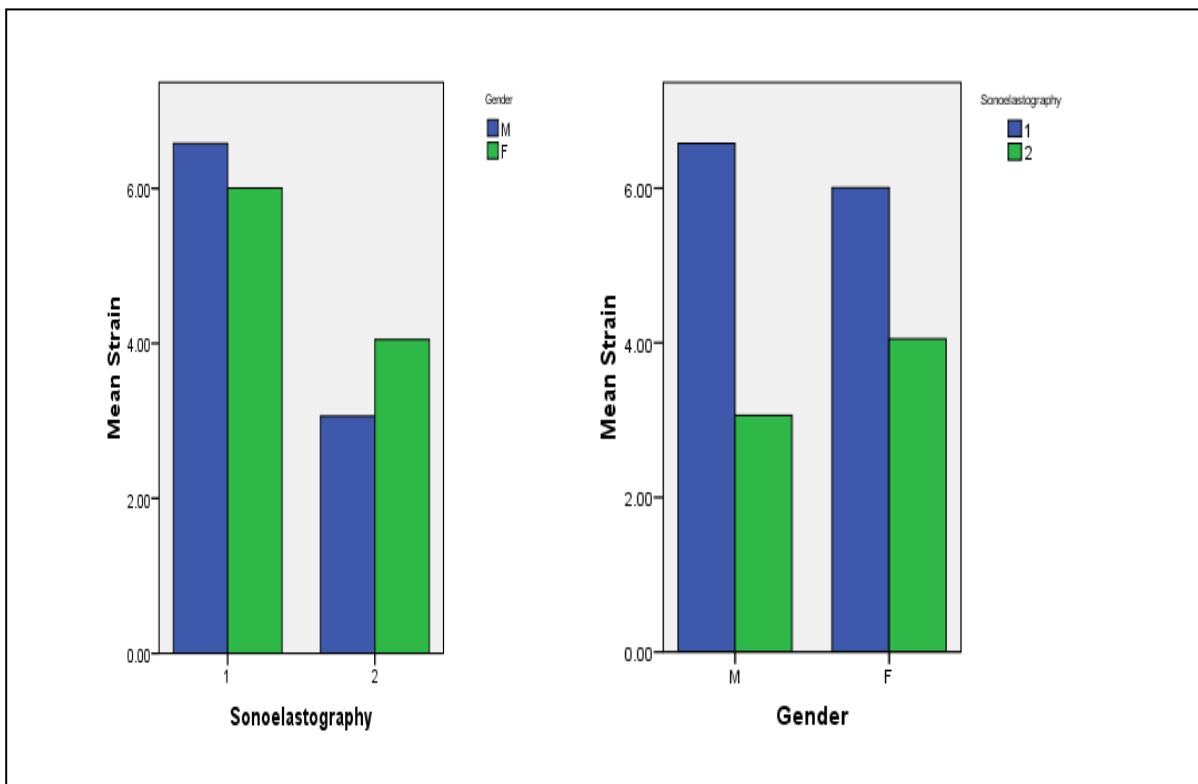


Figure 4.14: Bar charts of the mean strain of gender versus sonoelastographic grade.

4.3.8 Summary of mean strain indices

In the patients with positive results for tendinopathy, the strain value was much lower measuring $3.59 \pm 5.16SD$. The strain value was higher for patients with

negative results for tendinopathy (6.35 (\pm 2.52SD). The overall mean for all symptomatics was 5.05 (\pm 4.21 SD) as shown in Table 4.9.

Table 4.9: Summary of mean strain indices.

Mean strain values	Number	Group
5.05 (\pm 4.21 SD)	204	Symptomatic
3.59 (\pm 5.16 SD)	96	Positive symptomatic
6.35 (\pm 2.52 SD)	108	Negative symptomatic

4.3.9 Strain ratio as reference standard based on the ROC curve analysis

This research plotted a ROC curve and used it as a reference standard to compare the accuracy of diagnosis of tendinopathy in ultrasound and sonoelastography. How the curve was generated is described below.

4.3.9.1 The ROC curve

The ROC curve is defined as a plot of test sensitivity as the y coordinate versus its 1-specificity or false positive rate (FPR) as the x coordinate (Obuchowski, 2003; Park, Goo and Jo, 2004). It is an effective method of evaluating the performance of diagnostic tests (Obuchowski, 2003; Park, Goo and Jo, 2004). Sensitivity and specificity, which are defined as the number of true positives and the number of true negatives respectively, constitute the basic measures of performance of diagnostic tests. In situations where there are pairs of sensitivity and specificity values, the sensitivities and specificities depend on the cut-off levels that are used to define the positive and negative results. The ROC curve illustrates the relationship between sensitivity and FPR and displays the sensitivities and FPRs at all possible cut-off levels. Therefore, it can be used to assess the performance of a test independently of the decision threshold.

One of the most important measures of the ROC curve is the area under the ROC curve (AUC). The AUC is a measure of the overall performance of a diagnostic test and also a combined measure of sensitivity and specificity. The closer AUC is to 1, the better the overall diagnostic performance of the test. Also, the practical lower limit for the AUC of a diagnostic test is 0.5. The ROC is a good measure of test accuracy as it does not depend on the prevalence of disease or the cut points used to form the curve.

4.3.9.2 The Youden Index (J)

Disease diagnosis like tendinopathy by a biomarker such as strain ratio is dependent upon a correlation between strain ratio and disease state, whereby strain ratio values for a diseased population are different—usually higher—than in the corresponding non-diseased population. To use strain ratio for such classification, a cut-point c is established and individuals with values on one side of the cut-point are labelled as diseased and those with values on the other side are labelled non-diseased or healthy. The accuracy of such a classification can be determined by examining sensitivity (Se) and specificity (Sp), where Se and Sp are the probability of truly identifying diseased and non-diseased individuals respectively at a certain c . The strain ratio raw data of both asymptomatic and symptomatic participants were used in creating the ROC curve.

The ROC curve can be used to evaluate the effectiveness of a certain marker like the strain ratio in the determination of a diseased and non-diseased population. The ROC curve is a plot of (Se) versus (1-Sp) at all possible c (Ruopp, Perkins, Whitcomb & Schisterman, 2008).

This study established the highest probability of truly identifying diseased individuals, i.e., individuals with tendinopathy (Se) at a certain cut-point, c (the c for this study was 4.0 from the ROC curve). This defined the test sensitivity and typified the essence of this study as this method picked up the disease (tendinopathy) earlier than ultrasound.

The study also established the highest probability of truly identifying non-diseased individuals, i.e., individuals without tendinopathy (Sp) at a certain cut-point, c . This defined the specificity as it ruled out tendinopathy in these individuals.

One limitation in the application of the ROC curve is accounting for observations below some limit of detection resulting experimental error.

The Youden Index (J), the maximum potential effectiveness of a biomarker, is a common summary statistic of the ROC curve used in the interpretation and evaluation of a biomarker, which defines the maximum potential effectiveness of a biomarker. J can be formally defined as $J = \max_c \{Se(c) + Sp(c) - 1\}$. The cut-

point that achieves this maximum is referred to as the optimal cut-point (c^*) because it is the cut-point that optimizes the biomarker's differentiating ability when equal weight is given to sensitivity and specificity (Youden, 1950; Faraggi, 2000; Ruopp, Perkins, Whitcomb & Schisterman, 2008).

The Youden index establishes a value where the combined sensitivity and specificity are at their highest. It is a favourable option because, both parameters – sensitivity (Se) and specificity (Sp) – are important to the study. The study used strain ratio to classify a tendon as either tendinopathic or non-tendinopathic.

In order to use the strain ratio as reference standard to determine the accuracy of ultrasound and sonoelastography in the diagnosis of tendinopathy, a ROC curve analysis was used. The best cut-off strain ratio value was used to distinguish tendinopathy in all the patients in Study 2 of this research. In other words, it was used to suggest an optimal strain index criterion that was used to differentiate between normal and abnormal (tendinopathic) tendons, and obtain the best cut-off point for achieving maximum sensitivity and specificity. The ROC curve plotted represented the strain ratio values against normal and abnormal sonoelastography results. The resultant ROC is shown in Figure 4.15.

To find the cut-off point on the curve, the highest Youden Index was used. The Youden index was calculated as Sensitivity + Specificity – 1 (see Appendix H). From the Youden Index values, the highest value was 0.84 and gave a cut-off value of 4.0 for strain ratio. Therefore, the reference standard was based on a cut-off value of 4.0 on strain ratio, and subjects were categorized as either positive or negative for tendinopathy.

To measure the overall performance of this diagnostic test, the AUC was calculated which gave a value of 0.94 (95% confidence interval, 0.907 – 0.98; SE, 0.09). This value demonstrated a test with very high accuracy and sensitivity as 0.94 is closer to 1.0. The closer the AUC is to 1.0, the better the overall diagnostic performance of strain ratio test (Obuchowski, 2003). The result indicated the test has a good ability to discriminate between subjects with and without tendinopathy. Also, the lower bound of the 95% CI of AUC is far greater than 0.5, and therefore the test is statistically significantly better than making the

diagnostic decision based on pure chance (Obuchowski, 2003; Park, Goo & Jo, 2004).

From Figure 4.15, a cut-off value of 4.0 was used as the basis for reference standard in comparing diagnostic accuracy of ultrasound and sonoelastography. The ROC curve (blue line) is empirical. The chance diagonal (green line) has an ROC area of 0.5. The strain ratio test with an AUC of 0.94 which is greater than 0.5, has ability to discriminate between patients with and those without tendinopathy.

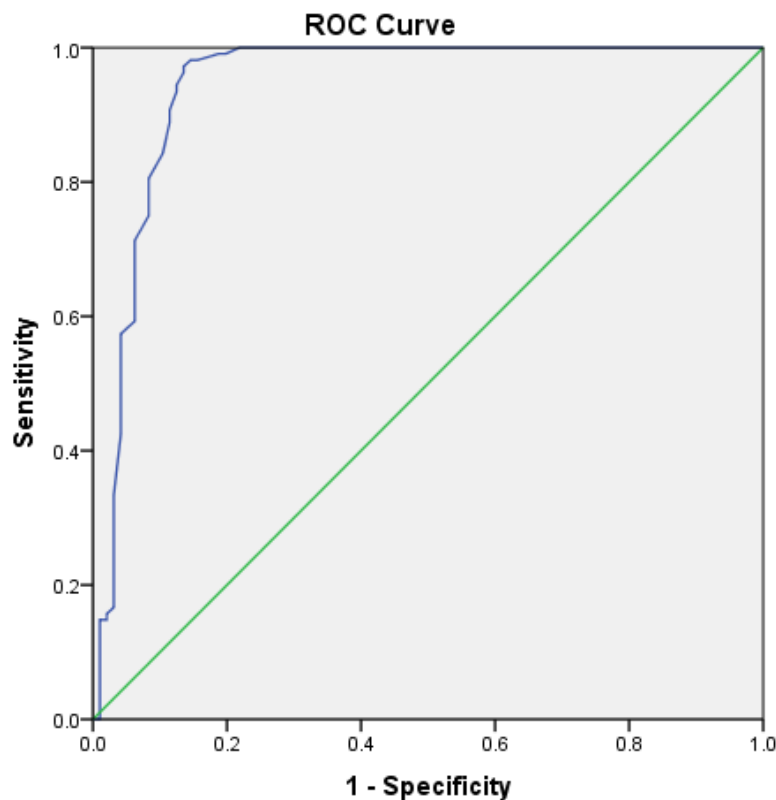


Figure 4.15: ROC curve of strain ratio of positive symptomatic supraspinatus tendons.

From the results of the AUC which has a value of 0.94, if we selected two patients at random, one with tendinopathy and one without, the probability is 0.94 that the patient with tendinopathy would have a more suspicious sonoelastographic result.

4.3.9.3 Cut-off points on the ROC curve

Table 4.10: Other cut-off points (strain ratio) on the ROC curve.

Strain ratio	Sensitivity (%)	Specificity (%)	1-Specificity (%) (FPR)	Youden Index Values
3.7	99	80	0.20	0.79
4.0	98	85	0.15	0.84
4.3	96	86	0.14	0.82
4.6	89	89	0.11	0.77
5.0	78	92	0.08	0.70
6.1	48	96	0.04	0.50
6.6	23	97	0.03	0.26
7.0	18	97	0.03	0.15

Table 4.10 shows several cut-off points on the ROC curve and the various sensitivity, specificity and FPR values for the diagnosis of supraspinatus tendinopathy at each cut-off level from the strain ratio values in this study. The sensitivities and specificities shown above depend on the strain ratio cut-off levels that the study used in defining positive and negative test results. As the cut-off level increases, the sensitivity decreases and the specificity increases, and vice versa.

4.3.10 Diagnostic accuracy of ultrasound using strain ratio as reference standard

The results of the diagnostic accuracy of ultrasound using strain ratio as reference standard are shown in Table 4.11. Ultrasound had good accuracy (68%) in categorizing participants on a cut-off point of 4.0 on the strain ratio scale ($p = 0.005$; χ^2 analysis). This resulted from its good ability to categorize both positive test (sensitivity = 73%) and negative test (specificity = 67%) results as shown in Table 4.12.

Table 4.11: Diagnostic accuracy of Ultrasound using Strain ratio as reference standard.

		Strain ratio	
		+ve ≤ 4.0	-ve >4.0
Ultrasound	Positive	29(14.2%)	55(27.0%)
	Negative	11(5.4%)	109(53.4%)

Table 4. 12: Details of 2x2 results for diagnostic accuracy of Ultrasound using Strain ratio as reference standard.

Variables	Values (confidence intervals)	Comments
Accuracy	68% (62-72%)	This is the proportion of patients correctly classified by US.
Sensitivity	73% (58-84%)	This is the proportion of patients with tendinopathy who have a positive test result.
Specificity	67% (63-69%)	This is the proportion of patients without tendinopathy who have a negative test result.
Positive Predictive Value (PPV)	35% (27-40%)	This value is the proportion of patients with a positive test result for tendinopathy who actually have tendinopathy.
Negative Predictive Value (NPV)	91% (86-95%)	This value is the proportion of patients with a negative test result for tendinopathy who do not have tendinopathy.
Positive Likelihood Ratio	2.2 (1.5-2.7)	This shows that a patient with tendinopathy is 2.2 times more likely to get a positive result than a person without tendinopathy.
Negative Likelihood Ratio	0.4 (0.2-0.7)	This shows that a patient with tendinopathy is 0.4 times less likely to get a negative result than a person without tendinopathy.

4.3.10 Kappa Measurement for Stage 2 ultrasound and strain ratio (cut-off 4.0)

In assessing the inter-rater agreement, the consistency of the diagnostic accuracy of two different diagnostic tests (ultrasound and strain ratio) was evaluated.

The *kappa* measure of agreement value was 0.28 with a significance of $p < 0.0005$. In this case the level of agreement between ultrasound and strain ratio was fair (Peat, 2001, p. 228 – value of 0.5 = moderate agreement; value of > 0.7 = good agreement; value of > 0.8 = very good agreement). Both modalities agreed in 67.6% of cases. They agreed that supraspinatus tendinopathy was present in 29 participants and absent in 109 participants. Disagreement occurred in 66 participants and agreement occurred in 148 patients.

4.3.11 Diagnostic accuracy of sonoelastography using strain ratio as reference standard

The diagnostic accuracy of sonoelastography using strain ratio as reference standard is shown in Table 4.13 in a 2x2 contingency table. Sonoelastography

had very high accuracy in categorizing participants using a cut-off point of 4.0 on the strain ratio scale ($p \leq 0.0001$; χ^2 analysis). This resulted from the excellent ability to categorize positive participants (sensitivity = 98%) and negative participants (specificity = 88%) as shown in Table 4.14. The negative predictive and positive values were 98% and 85% respectively.

There was very good agreement between sonoelastography and strain ratio in categorizing participants according to 4.0 cut-off point on ROC curve ($k = 0.84$), with the modalities agreeing in 92.2% of cases. Both modalities agreed that supraspinatus tendinopathy was present in 82 participants and absent in 106 participants. Disagreement occurred in 16 participants.

The chi-square test for independence carried out on this data was very highly significant at 0.001 level (2-tailed, $p < 0.0005$) of significance. ($\chi^2 = 122.22$, $df = 1$). So it can be inferred that there is a very highly significant agreement between sonoelastography and strain ratio in categorizing participants. Therefore the association between sonoelastography and strain ratio is considered to be extremely statistically significant.

Table 4.13: Diagnostic accuracy of Sonoelastography using Strain ratio as reference standard.

		Strain ratio	
		+ve ≤ 4.0	-ve >4.0
Sonoelastography	Positive	82(40.2%)	14(6.9%)
	Negative	2(0.9%)	106(52.0%)

Table 4.13 shows the diagnostic properties (positives and negatives) of individual tests in the supraspinatus tendons when strain index of 4.0 was used as the cut-off point to determine the presence or absence of tendinopathy.

Table 4.14: Details of 2x2 results for diagnostic accuracy of Sonoelastography using Strain ratio as reference standard.

Variables	Values (confidence intervals)	Comments
Accuracy	92% (88-94%)	This is the proportion of patients correctly classified by SE.
Sensitivity	98% (92-100%)	This is the proportion of patients with tendinopathy who have a positive test result.
Specificity	88% (85-90%)	This is the proportion of patients without tendinopathy who have a negative test result.
Positive Predictive Value (PPV)	85% (81-87%)	This value is the proportion of patients with a positive test result for tendinopathy who actually have tendinopathy.
Negative Predictive Value (NPV)	98% (94-100%)	This value is the proportion of patients with a negative test result for tendinopathy who do not have tendinopathy.
Positive Likelihood Ratio	8.4 (5.9-9.7)	This shows that a patient with tendinopathy is 8.4 times more likely to get a positive result than a person without tendinopathy.
Negative Likelihood Ratio	0.03 (0.01-0.09)	This shows that a patient with tendinopathy is 0.03 times less likely to get a negative result than a person without tendinopathy.

4.3.12 Kappa measurement for Stage 2 sonoelastography and strain ratio (cut-off 4.0)

In assessing the inter-rater agreement, the consistency of the diagnostic accuracy of two different diagnostic tests (sonoelastography and strain ratio) was evaluated.

The *kappa* measure of agreement value was 0.84 with a significance of $p < 0.0005$. In this case the level of agreement between sonoelastography and strain ratio was very good (Peat, 2001, p. 228 – value of 0.5 = moderate agreement; value of > 0.7 = good agreement; value of > 0.8 = very good agreement).

4.3.13 Comparison of the diagnostic accuracy of sonoelastography and ultrasound using clinical diagnosis as reference standard

The results of the diagnostic accuracy of sonoelastography and ultrasound are shown in Table 4.15. Both sonoelastography and ultrasound were accurate in classifying the participants using clinical diagnosis as the reference standard ($p < 0.001$, χ^2 analyses). However, sonoelastography showed slightly better accuracy than ultrasound (65% vs 59%, $p < 0.001$). Sonoelastography achieved greater accuracy over ultrasound because of its ability to better categorize positive

participants (sensitivity = 75% vs 65%, $p < 0.001$). Sonoelastography was better than ultrasound in categorizing negative participants (specificity = 63% vs 57%, $p < 0.001$).

The chi-square test for independence was carried out to ascertain the degree of association between sonoelastography and ultrasound. The result on this data was significant at 0.001 level (2-tailed $p < 0.0005$) of significance. ($\chi^2 = 36.83$, $df = 1$). So we conclude that there was a significant agreement between US and SE in categorizing participants.

Table 4.15: Diagnostic accuracy of Sonoelastography and Ultrasound in supraspinatus tendinopathy using Clinical diagnosis as reference standard.

Variable	SE (confidence interval)	US (confidence interval)
Accuracy (%)	65% (59-70%)	59% (53-64%)
Sensitivity (%)	75% (60-86%)	65% (50-78%)
Specificity (%)	63% (59-66%)	57% (54-61%)
Positive Predictive Value (%)	33% (26-38%)	27% (21-33%)
Negative Predictive Value (%)	91% (86-95%)	87% (81-92%)
Positive Likelihood Ratio	2.0 (1.5-2.5)	1.5 (1.1-2.0)
Negative Likelihood Ratio	0.4 (0.2-0.7)	0.6 (0.4-0.9)

Using strain ratio as the reference standard, sonoelastography showed a higher positive predictive value (PPV) than ultrasound; 85% against 35%. Sonoelastography also showed a slightly higher negative predictive value than ultrasound (98% against 91%).

Using clinical diagnosis as the reference standard, sonoelastography showed a higher positive predictive value (PPV) than ultrasound; 33% against 27%. Sonoelastography also showed a slightly higher negative predictive value (NPV) than ultrasound (91% against 87%).

4.3.14 Comparison of diagnostic accuracy of sonoelastography and ultrasound using strain ratio as reference standard

The results of the diagnostic accuracy of sonoelastography and ultrasound are shown in Table 4.16 demonstrating the accuracy, specificity, sensitivity, and

negative and positive predictive values, and positive and negative likelihood ratios for sonoelastography and ultrasound for predicting diagnostic accuracy of supraspinatus tendinopathy using strain ratio as the reference standard ($p < 0.001$, χ^2 analyses). Nevertheless, the accuracy of sonoelastography was far superior to that of ultrasound (92% vs 68%, $p < 0.001$). Sonoelastography achieved greater accuracy over ultrasound because it has a better ability to categorize positive participants or tests (sensitivity = 98% vs 73%, $p < 0.001$). Also sonoelastography was superior to ultrasound in categorizing negative participants or tests (specificity = 88% vs 67%, $p < 0.001$).

Table 4.16: Diagnostic accuracy of Sonoelastography and Ultrasound using Strain ratio as reference standard.

Variable	SE (confidence interval)	US (confidence interval)
Accuracy (%)	92% (88-94)	68% (62-72%)
Sensitivity (%)	98% (92-100)	73% (58-84%)
Specificity (%)	88% (85-90)	67% (63-69%)
Positive Predictive Value (%)	85% (81-87)	35% (27-40%)
Negative Predictive Value (%)	98% (94-100)	91% (86-95%)
Positive Likelihood Ratio	8.4 (5.9-9.7)	2.2 (1.5-2.7)
Negative Likelihood Ratio	0.03 (0.01-0.09)	0.4 (0.2-0.7)

Though there was differences in accuracy, there was very good agreement in the positive test group in sonoelastography and strain ratio ($k = 0.84$) and fair agreement in ultrasound ($k = 0.28$).

4.3.14 Measure of agreement between ultrasound and sonoelastography

It is important to ascertain if there is a relationship between ultrasound appearances and sonoelastographic values. The consistency of two different diagnostic tests, ultrasound and sonoelastography, in classifying the supraspinatus tendons as normal and abnormal, is assessed using *kappa* measure of agreement. This is a non-parametric test which requires two categorical variables and equal number of categories (normal tendon =1, abnormal tendon = 2). It assumes equal number of categories from the two tests. The aim here is to see if the tendons classified as normal or abnormal using ultrasound were also classified as normal or abnormal using sonoelastography.

Both ultrasound and sonoelastography agreed that 51.0% (104) were positive and 36 (17.6%) were negative. While ultrasound showed 29.4% (60) to be positive, sonoelastography demonstrated them as negative. Both modalities did not agree on 31.4% (64) of cases: 4 (2.0%) were false positive and 60 (29.4%) were false negative. Total agreement was 68.6% (140) and total disagreement was 31.4% (64).

In conclusion, from the data above, the *kappa* measure of agreement value was 0.35 with a significance of $p < 0.001$. This is a fair agreement (Landis and Koch, 1977).

Also, there was a strong positive correlation between ultrasound and sonoelastography, $R = 0.43$, $n = 204$, $p = 0.0005$.

4.3.15 Measure of agreement between symptomatic and asymptomatic groups

To find out whether there is a significant statistical difference between symptomatic and asymptomatic groups, an independent samples *t*-test was conducted to compare the strain ratio values of both groups. There was a significant statistical difference in the mean score for the asymptomatic ($M = 1.06$, $SD = 0.232$) and symptomatic ($M = 1.64$, $SD = 0.482$); $t(160) = 13.52$, $p = 0.0005$ (two-tailed).

Table 4.17: Comparison of diagnostic accuracy of Sonoelastography and Ultrasound using Strain ratio and Clinical diagnosis as reference standards (values are in percentages).

Variables	SR		CD	
	SE	US	SE	US
Accuracy (%)	92	68	65	59
Sensitivity (%)	98	73	75	65
Specificity (%)	88	67	63	57
Positive Predictive Value (%)	85	35	33	27
Negative Predictive Value (%)	98	91	91	87
Positive Likelihood Ratio	8.4	2.2	2.0	1.5
Negative Likelihood Ratio	0.03	0.4	0.4	0.6

Table 4.17 shows all the different parameters or variables that were used to assess diagnostic accuracy of sonoelastography and ultrasound using clinical

diagnosis and strain ratio as reference standards. From the figures it is seen that sonoelastography proved a better modality in obtaining better accuracy, sensitivity and specificity, and positive and negative predictive values than ultrasound using strain ratio and clinical diagnosis as reference standards.

4.3.16 Summary of findings

In patients with positive results for tendinopathy, the mean strain value was low measuring $3.59 \pm 5.16SD$. There was statistically significant difference in the mean strain ratio values for males and females. This meant that more males presented with softer tendons (or tendinopathy) than females.

A receiver operating characteristic (ROC) curve was plotted to find a cut-off value to indicate pathology. A cut-off value of 4.0 was read off on the highest scale on the Youden index corresponding to 0.84. Therefore, the reference standard was based on cut-off of 4.0 on strain ratio, and subjects were categorized as either normal or abnormal if the value of their strain ratio on the ROC was either higher or lower than 4.0. The area under the curve was 0.94 and demonstrated a test with very high accuracy and sensitivity. Other several cut-off points on the ROC curve and the various sensitivity, specificity and FPR values for the diagnosis of supraspinatus tendinopathy at each cut-off level from the strain ratio values were noted in the study.

In symptomatic participants, a total of 108 (52.9%) of supraspinatus tendon showed Grade 1 colour pattern, 51 (25%) demonstrated Grade 2 and Grade 3 was seen in 45 (22.1%) tendons. The tendon elastographic pattern was very easily visible. The tendons showed a characteristic blue-green pattern predominantly. This was evident in 108 (52.9%) tendons and corresponded to Grade 1 colour pattern. This is an indication of hard tissue or normal appearance of the supraspinatus tendon. A total of 51 (25%) tendons showed evidence of yellow colouration within the tendons in keeping with Grade 2 colour pattern. This is an indication of intermediate tissue softening. A total of 45 (22.1%) tendons demonstrated evidence of red colouration in keeping with soft tissue pattern. In total, 96 (47.1%) tendons demonstrated evidence of tendinopathy.

The two reference standards used for this study were clinical diagnosis and strain ratio. The diagnostic accuracy of ultrasound and sonoelastography using the two reference standards were assessed and compared.

Using clinical diagnosis as the reference standard, sonoelastography showed slightly better accuracy than ultrasound (65% vs 59%, $p < 0.001$). Sonoelastography achieved greater accuracy over US because of its ability to better categorize positive participants (sensitivity = 75% vs 65%, $p < 0.001$). Sonoelastography was also better in categorizing negative participants (specificity = 63% vs 57%, $p < 0.001$). The *kappa* measure of agreement between ultrasound and sonoelastography was fair with a value of 0.35 and a significance of $p < 0.0005$. The chi-square test concluded that there was a significant agreement between ultrasound and sonoelastography in categorizing participants.

Using strain ratio as the reference standard, the accuracy of sonoelastography was far superior to that of ultrasound (92% vs 68%, $p < 0.001$). Sonoelastography achieved greater accuracy over ultrasound because it has a better ability to categorize positive participants or tests (sensitivity = 98% vs 73%, $p < 0.001$). Also sonoelastography was superior to ultrasound in categorizing negative participants or tests (specificity = 88% vs 67%, $p < 0.001$).

4.4 Discussion

This section has been structured into different sub units. Each unit deals with specific outcomes from the results obtained. It begins with a discussion on the sensitivity, specificity, PPV, NPV and accuracy of sonoelastography where the aim was to measure the strain ratio of supraspinatus and assess the accuracy of sonoelastography. A detailed comparison of this current study with a closely related research identified in the literature review has also been undertaken in this section. Similar comparison of the various studies with different sample sizes in sonoelastography studies has been undertaken in this section. A close review of the outcome of ROC curve assessment and accuracy measurement and strain ratio has also been undertaken in this section. The diagnosis of tendinopathy, diagnostic reference standard as well as issues relating to blinding and biases –

selection, measurement and analysis have all been discussed in this section. It concludes by reflecting on the limitations of this study bearing in mind all the different variables and factors examined in this research.

4.4.1 Sensitivity, specificity, PPV, NPV and accuracy

The aim of this study was to measure the strain ratio of supraspinatus tendon and use the values to assess the accuracy of sonoelastography when compared with ultrasound in the diagnosis of supraspinatus tendinopathy in patients with shoulder pain. The findings of this study were compared and contrasted with other studies that compared the accuracy of sonoelastography and ultrasound. The established reference standard for the diagnosis of tendinopathy is ultrasound but ultrasound has its own limitation as it cannot measure tissue alterations in tendons. The current study results showed that sonoelastography demonstrated higher accuracy of 92% in comparison with 68% of ultrasound, higher sensitivity – 98% vs 73%, and specificity – 88% vs 67%, in the diagnosis of tendinopathy.

The results of this study agreed with the results of earlier studies. The study by De Zordo *et al.*, (2007b) showed a significantly higher detection of intratendinous colour alterations by sonoelastography (yellow, red) in comparison to focal lesion detection by grey scale ultrasound ($p < 0.001$) in extensor tendon insertion of 15 consecutive patients. In a separate but similar study by Abdel Razek & Ezzat (2008), the sensitivity and NPV was increased from 95% to 97% and from 87% to 93% respectively by adding sonoelastography to conventional ultrasound technique. These results are in agreement with the present result. The NPV value of the present study was comparable as the value increased from 91% to 98% when sonoelastography was added to the ultrasound technique.

A similar review of a study on Achilles tendons of 25 patients by De Zordo *et al.* (2008) showed alterations in 61% of clinical examinations, in 59% of US images and in 68% of sonoelastography images. Sonoelastography showed sensitivity of 94%, specificity of 99%, and accuracy of 97%, while ultrasound showed sensitivity of 93%, specificity of 100% and accuracy of 99% (De Zordo *et al.*, 2008). The outstanding characteristic of the present study was the inclusion of strain ratio as a reference standard in addition to ultrasound and clinical

diagnosis. These studies used only clinical diagnosis and ultrasound as reference standard, except in the study by Abdel Razek & Ezzat (2008) and De Zordo *et al.* (2007a) where MRI and clinical diagnosis were used as reference standard.

This current study results also showed that sonoelastography had better negative predictive value than ultrasound where NPV of 91% was obtained on sonoelastography compared to 87% in ultrasound. A critical reflection has shown that the probability that tendinopathy is absent when the test result is absent is better with sonoelastography. This assertion was corroborated by De Zordo *et al.* (2009a) in a study on patient complaining of lateral epicondylitis which showed higher sensitivity and NPV on sonoelastography than with ultrasound (De Zordo *et al.*, 2009a). Their results showed 100% NPV in sonoelastography and 95% in ultrasound. From the figures, they obtained better NPV and sensitivity (100% versus 98%) than the present study possibly due to the smaller sample size of their study.

Using sonoelastography, a sensitivity of 100%, a specificity of 89%, an accuracy of 94%, a positive predictive value of 88% and a negative predictive value of 100% was found, whereas ultrasound showed a sensitivity of 95%, a specificity of 89%, an accuracy of 91%, a positive predictive value of 88% and a negative predictive value of 95% (De Zordo *et al.*, 2009a).

A comparison of this current study with the work of Abdel Razek & Ezzat (2008) which investigated supraspinatus tendon with sonoelastography revealed some important variables. This current study had a larger patient sample size of 204 compared to 40 by Abdel Razek & Ezzat (2008) which was significant. A reflection on the similarities of both studies revealed that a similar ultrasound machine was used, both results had statistically significant difference in tendon stiffness between healthy volunteers and patients ($p < 0.001$), both studies showed increased sensitivity and NPV when sonoelastography was added to ultrasound, and none of the two studies considered the effect of side dominance. In contrast, while the current study established strain ratio for the volunteers and patients and investigated only tendinopathy, Abdel Razek & Ezzat (2008) in their study in addition examined tendon tears. The details of the similarities and

differences in both studies are shown in Table 4.18.

Table 4.18: Comparison between the current study and Abdel Razek & Ezzat's study.

Ohuegbe, 2014	Abdel Razek & Ezzat, 2008
Similarities	
1. Hitachi EUB-7500, L54M, 6 -13 MHz probe.	Hitachi EUB-7500, L54M, 6 -13 MHz probe.
2. The differences in tendon stiffness between the healthy volunteers and the patients were statistically significant ($p < 0.0001$).	The differences in tendon stiffness between the healthy volunteers and the patients were statistically significant ($p < 0.0001$).
3. The sensitivity and NPV increased from 95% to 97% and from 87% to 93% respectively by adding elastography to the conventional ultrasound technique.	The sensitivity and NPV increased from 73% to 98% and from 91% to 98% respectively by adding elastography to the conventional ultrasound technique.
4. In the 284 healthy volunteers, elastography showed blue and green colour in 85.7% of the tendons consistent with stiff normal tendon tissue, and ultrasound showed 95.8% of the tendons which is consistent with normal findings at grayscale.	In the 20 healthy volunteers, elastography showed blue colour throughout the tendon (100%), which is consistent with stiff normal tendon tissue and normal findings at grayscale.
5. Study did not consider dominant side.	Study did not consider dominant side.
Differences	
1. 284 healthy volunteers and 204 supraspinatus tendons in painful shoulders clinically suspected of tendinopathy.	Studied 20 healthy volunteers and 40 patients presenting with shoulder pain.
2. The elastography findings were compared with ultrasound results, clinical diagnosis and strain ratio.	The elastography findings were compared with the ultrasound results.
3. No MRI comparison.	For 20 patients, elastography was also compared with MRI findings.
4. The study did not examine tendon tears but purely tendinopathy.	8. The study examined tendon tears.
5. Established strain ratio for normal tendons and for abnormal tendons; created a cut-off SR value of 4.0 to indicate or exclude SST tendinopathy.	Did not investigate or use strain ratio in their study.

The advantage of using studies with large sample sizes was seen in a detailed review that compared the sample size of the current study with that of previous studies as emphasized in the literature review in chapter 2. Relative to this current study which has a sample size of 204 supraspinatus tendons, a sample size of 18 was used in a study of the Achilles tendon by Klauser *et al.* (2006). A sample size of 50 was also used in another study of the Achilles tendon by De Zordo *et al.*, (2007a), and 40 in the research on the supraspinatus tendon by

Abdel Razek & Ezzat, (2008). These are reflected in Table 4.19. A critical reflection of the different samples sizes of different studies indicate that studies of large sample sizes give more reliable results or better precision than smaller sizes in diagnostic study (Biau, Kerneis & Porcher, 2008).

Table 4 19: Comparison of sample sizes of Sonoelastography studies of tendons with the current study.

Authors/Year	Sample size
1. Klauser <i>et al.</i> , 2006	15 patients with 18 painful Achilles tendons and 18 tendons in sex and age matched healthy volunteers.
2. De Zordo <i>et al.</i> , 2007a	50 Achilles tendons in 25 consecutive patients with unilateral complains and 50 Achilles tendons in 25 healthy sex age matched volunteers were examined. 22/25 patients underwent MRI.
3. De Zordo <i>et al.</i> , 2007b	15 consecutive patients and 15 sex and age matched healthy volunteers by using RTSE and compared it to findings in gray scale sonography.
4. Abdel Razek & Ezzat, 2008	Studying 20 healthy volunteers and 40 patients presenting with shoulder pain.
5. De Zordo <i>et al.</i> , 2008	Achilles tendons of 25 consecutive patients (11 men, 14 women; mean age, 55 years; range, 37-79 years) and 25 healthy volunteers (11 men, 14 women; mean age, 46 years; range 25-76 years).
6. De Zordo <i>et al.</i> , 2009	In a prospective analysis 38 elbows of 32 consecutive patients (10 men, 22 women; mean age, 52.63 years; range, 38-70 years) complaining of lateral epicondylitis and 44 asymptomatic elbows of 28 healthy volunteers (11 men, 17 women; mean age, 43.64 years; range, 24 - 89 years) were assessed by clinical examination, US, PDUS and SE.
7. Klauser <i>et al.</i> , 2009a	Examined 80 Achilles tendons in healthy volunteers and 25 tendons in patients complaining of inflammation and pain in the Achilles region (achillodynia).
8. Klauser <i>et al.</i> , 2009b	38 elbows from patients with clinically suspected tennis elbow and 44 asymptomatic elbows.
9. Ohuegbe, 2014 (thesis)	204 supraspinatus tendons in painful shoulders clinically suspected of tendinopathy.

Using clinical diagnosis as the reference standard in this research, the accuracy of sonoelastography was 65% with a sensitivity of 75% and specificity of 63%. These values are lower when compared to the study by De Zordo *et al.* (2010) which showed accuracy of 97%, sensitivity of 94% and specificity of 99% also using clinical diagnosis as reference standard. There is a doubt if the difference in sample size could have contributed to the significant difference in the results: the current study used 284 supraspinatus tendons and De Zordo's study had a sample size of 25. One possible explanation for a potential cause of low

specificity in the current study is that a variety of pathologic imaging findings could be present before the start of symptoms, leading to false-positive findings if clinical examination is the reference standard.

Sonoelastography was found to increase the detection of intratendinous alterations and facilitated differentiation between healthy and symptomatic supraspinatus tendons in the current study. The results showed sensitivity of 98%, specificity of 88%, and accuracy of 92% when strain ratio was used as reference standard. Using clinical diagnosis as reference standard, sensitivity of 75%, specificity of 63%, and accuracy of 65% were obtained. In comparison with the study by De Zordo *et al.* (2009c) on healthy and symptomatic extensors origin tendon, the results of the current study exhibited lower values. The study by De Zordo showed sensitivity of 100%, specificity 89%, and accuracy 94% using clinical diagnosis as the reference standard.

Correspondingly, the current study had a comparable result with sonoelastographic sensitivity of 98%, specificity of 88%, and accuracy of 92%. Similarly, using sonoelastography to investigate the Achilles tendon, De Zordo *et al.* (2010c) found a sensitivity of 94 %, specificity of 99 %, and accuracy of 97 % when clinical diagnosis was used as the reference standard.

In a different study on the breast by Yerli, Yilmaz, Kaskati & Gulay, (2011), the authors were of the opinion that elasticity scoring and strain index methods have comparable diagnostic potential for differentiating between benign and malignant breast lesions as one would between normal and pathological tendons. Likewise, sonoelastography was seen in the current study to differentiate normal from pathologic tendons where the tendons of asymptomatic volunteers and symptomatics showed characteristic yellow and red colourations in keeping with tendinopathy. Therefore it can be hypothesized that supraspinatus tendinopathy is associated with significant softening of intratendinous tissue as shown in the current study. This finding is in agreement with reports of other eminent authors such as Drakonaki, Allen & Wilson (2009), De Zordo *et al.* (2009a), De Zordo *et al.* (2010) and Klauser *et al.* (2009a).

The findings in the sonoelastograms of the current study demonstrated features like subacromial-subdeltoid bursitis, subscapularis bursitis, long head of biceps

tendinopathy and/or tenosynovitis, osteoarthritis of the acromioclavicular joint on images. These imaging findings are known to mimic clinical presentations of tendinopathy. In the author's opinion, it was possible that this made it difficult to clinically exclude tendinopathy from clinical signs of impingement in some patients. These features could have been confounders in the present study and affected the sensitivity and accuracy of the current study, and prognostically linked to the outcome of the final results. This may have led to uneven distribution in the study sample. This opinion is upheld by Obuchowski (2003) and Lewis (2009) in their review papers. However, as the sample selection was consecutive, both known and unknown confounders may have been randomly distributed in order to reduce its effect on the study.

Statistical analysis of the current study also showed strong statistical agreement of sonoelastography with strain ratio ($k = 0.84$), and higher accuracy when both methods were combined. In line with the finding, a study by De Zordo *et al.* (2007a) had similar result where sonoelastography showed good correlation with ultrasound ($p < 0.001$, $R = 0.864$) and MRI ($p < 0.001$, $R = 0.844$). However, the present study did not compare with MRI. In another separate study on common extensors origin tendon, but with similar findings to the current study, De Zordo *et al.* (2009) showed that sonoelastography had good correlation to ultrasound findings ($R > 0.900$). Correlation (R) between sonoelastography and ultrasound was 0.89 in a study on Achilles tendon by De Zordo *et al.* (2008) which emphasized the results of current study. Correlation with ultrasound findings was good once again ($R = 0.900$) in another study (Klauser *et al.*, 2009a).

In the current study, the high PPV of sonoelastography (85%) indicated that the technique correctly showed the proportion of patients with a positive test result for tendinopathy who actually have the disease (Akobeng, 2006). This was not a chance occurrence but an indication of the reliability of the new test. PPV is known to be determined by the test's sensitivity, specificity and prevalence of the disease condition for which strain ratio was used. The clinical implication is that the higher the prevalence, the higher the PPV and the more likely a positive result is able to predict the presence of disease. In other words, sonoelastography was vastly improved and more able to predict the presence of tendinopathy (85%) compared to ultrasound (35%) in this study. The result of

this study is comparable to PPV values of 88% in sonoelastography in the investigation of the common extensors origin tendon in the elbow (De Zordo *et al.*, 2009c).

4.4.2 ROC curve and accuracy measurement

The current study is the first large study of asymptomatic and symptomatic SSTs with a wider age range comparing sonoelastography and ultrasound. It is the first study that has used the ROC curve to create a cut-off point which was used as a reference standard. It also compared the accuracy of both modalities using clinical diagnosis and strain ratio as reference standards with results that could be used as benchmark for future studies.

The current study confirmed the premise that sonoelastography can aid accurate diagnosis because of its capability to measure tendon elasticity. Using strain ratio as the reference standard and a cut-off point of 4.0, the accuracy of sonoelastography was far superior to that of ultrasound (92% vs 68%, $p < 0.001$). Sonoelastography achieved greater accuracy over ultrasound because it was able to categorize positive participants better (sensitivity = 98% vs 73%, $p < 0.001$). Also sonoelastography was superior to ultrasound in categorizing negative participants (specificity = 88% vs 67%, $p < 0.001$).

Furthermore, in a similar study by Choi *et al.* (2011) on the breast that substantiated the findings of the current study, the diagnostic utility of sonoelastography in differentiating reactive and metastatic axillary lymph nodes in breast cancer was evaluated. The results revealed that sonoelastography increased the sensitivity of grey-scale ultrasound in the detection of metastatic axillary lymph nodes from 74.2% (ultrasound) to 80.7% (sonoelastography). In addition, the study showed that combined ultrasound and sonoelastography showed higher sensitivity (87.1%) and lower specificity (54.6%) than ultrasound alone. The specificity of ultrasound was 78.8% and that of sonoelastography was 66.7%. With a strain ratio cut-off point of 2.3, sensitivity was 82.8%, and specificity was 56.3% (Choi *et al.*, 2011). This study used fat-tissue as reference and a strain ratio of greater than 2.3 was useful for differentiating metastatic axillary lymph nodes.

In line with achieving the objective of the current study as stated in the study objectives in chapter one, an area under ROC curve of 0.94 (95% confidence interval, 0.907–0.98; SE, 0.09) was obtained in the current study. This value was created using strain ratio values. Its critical analysis demonstrated a test with very high accuracy and sensitivity, and it indicated the test has a good ability to discriminate between subjects with and without tendinopathy. According to Garra (2011), quantification is one of the recent advances in SE and it has found use in strain ratio, acoustic radiation force impulse imaging, and shear wave velocity estimation. No published study at present has shown any ROC curve for supraspinatus or any other tendon. The current result is comparable to results of summary ROC curves in a meta-analysis (de Jesus *et al.*, 2009) obtained for MR arthrography, MRI, and ultrasound for all supraspinatus tendon tears with respective values of area under the ROC curve. Their results indicated that the area under ROC curve was highest for MR arthrography (0.935), followed by ultrasound (0.889) and then MRI (0.878). There were no significant differences in either sensitivity or specificity between MRI and ultrasound in the diagnosis of partial- or full-thickness rotator cuff tears in the study ($p > 0.05$) (de Jesus *et al.*, 2009). In line with the above results, another study showed area under the receiver operating characteristic (ROC) curve of 0.88 to 0.95 for distinguishing cancer from benign lesions in the breast (Garra, 2011). Table 4.20 shows area under ROC curve values for different tissues; the values are seen to be comparable to present study result.

Table 4.20: Area under ROC curve values for different tissues.

Tissue	Area under ROC curve values
Ultrasound (RC tears)	0.88 (de Jesus <i>et al.</i> , 2009)
MRI Arthrography (RC tears)	0.94 (de Jesus <i>et al.</i> , 2009)
MRI (RC tears)	0.89 (de Jesus <i>et al.</i> , 2009)
Breast	0.88–0.95 (Garra, 2011)
Thyroid	0.92 (Xing <i>et al.</i> , 2011)
Breast (SR)	0.84 (Yerli <i>et al.</i> , 2011)
Breast – 5-point scoring	0.86 (Yerli <i>et al.</i> , 2011)
Supraspinatus tendon (SR)	0.94 (Ohuegbe, thesis)

MRI – magnetic resonance imaging; RC – rotator cuff; SR – strain ratio

4.4.3 Strain ratios

In patients with positive results for tendinopathy, the mean strain value was lower measuring 3.59 ± 5.16 (SD). There are no existing published values in tendon sonoelastography to compare these values with. However, based on the established reference cut-off value of 4.0 on the ROC curve, the value of 3.59 is in keeping with definition of tendinopathy. There was statistically significant difference in the mean strain ratio values in this study for males and females ($t(282) = 2.35, p = 0.02$ (two-tailed)). This could suggest that more males are susceptible to softer tendons (or tendinopathy) than females. A study by Maffulli, Wong & Almekinders (2003) confirmed this finding and maintained that Achilles tendon tears occur 4 to 7 times more often in males than females as tendons deteriorate with age.

A recent study on “sonoelastography findings of supraspinatus tendon in rotator cuff tendinopathy without tear: comparison with magnetic resonance images and conventional ultrasonography” showed that sonoelastography is invaluable in the detection of the intratendinous and peritendinous alterations of the supraspinatus tendon (Seo, Yoo and Ryu, 2014). While this study compared sonoelastography to MRI and grey-scale ultrasound, this current study compared with sonoelastography and strain ratio values. The introduction of quantitative measurement in the current study appears to demonstrate superiority over grey-scale ultrasound, which in turn is superior to MRI; also, the limitations of MRI in imaging tendinopathy are evident in literature.

4.4.4 Diagnosis of Tendinopathy

There is literature evidence that MRI is currently the gold standard for diagnosis of shoulder pathology, but has limited availability, is expensive and has very restricted role when dealing with tendinopathy (Richards, Dheer & McCall, 2001; Shalabi *et al.*, 2007; Fredberg & Stengaard-Pedersen, 2008). In a meta-analysis by de Jesus *et al.* (2009) that compared the sensitivity and specificity of ultrasound with MRI, no significant differences ($p < 0.05$) were seen between the two modalities. The study revealed same sensitivity of 85% in all tears for MRI and ultrasound (de Jesus *et al.*, 2009).

In the study on 'comparative accuracy of magnetic resonance imaging and ultrasonography in confirming clinically diagnosed patellar tendinopathy', Warden *et al.* (2007) showed that ultrasound demonstrated better accuracy than MRI in confirming clinically diagnosed tendinopathy (accuracy – 82% vs 70%; sensitivity – 87% vs 57%; specificity – 82% vs 82%), (Warden *et al.*, 2007). Based on recent facts, ultrasound is the preferred and first line choice in all cases of clinically diagnosed tendinopathy. It is the preferred choice to MRI for monitoring resolution of pathology when there is no encouraging improvement with treatment. However, the current study has shown that sonoelastography and strain ratio were more accurate and sensitive than ultrasound. Sonoelastography was considered to have better visual resolution (as spelt out in chapter one) than ultrasound due to its ability to measure and demonstrate tissue elasticity as exemplified in the accuracy and sensitivity results of the current study. Using clinical diagnosis as reference standard, sonoelastography showed a higher sensitivity of 75% compared to ultrasound, 65%. Also, using strain ratio as the reference standard, sonoelastography had a sensitivity of 98% compared to 73% shown by ultrasound. Accuracy of sonoelastography was 92% versus 68% of ultrasound.

In symptomatic participants, the current study presented three sonoelastographic colour grading patterns that were used to indicate either normal or pathologic changes. Grade 2 and grade 3 patterns were indicative of tendon softening with evidence of yellow and red colourations respectively that make up 47.1% (96/204) within the tendons. The results reflected the established colour grade findings of Frey (2003) on which this study was based on. Other tendon studies showed similar results. Patients showed Grade 3 in 64% (16/25) of the distal part, in 80% (20/25) of the mid-portion, and 28% (7/25) of the proximal part in a study on Achilles tendon (De Zordo *et al.*, 2007). Real-time sonoelastography of common extensors origin tendon showed softening of different grades in 67%, a statistically significant difference in relation to the findings in healthy volunteers ($p < 0.001$) (De Zordo *et al.*, 2009a). Also, in a separate study on the Achilles tendon De Zordo *et al.* (2008) found alterations in the tendons in 68% of sonoelastography images. Furthermore in another study, distinct softening was found in 57 % and mild softening in 11 % of Achilles tendons (De Zordo *et al.*,

2010). A thorough review of the above studies displayed a common denominator: it was easy to make a diagnosis of tendinopathy based on colour change which was consistent with tissue softening. Therefore, tissue softening or hardening served as a useful tool to characterize an intratendinous lesion or peritendinous involvement in the tendon as established by previous authors (De Zordo *et al.*, 2009a; Khoury, Cardinal & Brassard, 2008; Drakonaki, Allen & Wilson, 2009; Abdel Razek & Ezzat, 2008; Trombetti, 2008; Schreiber *et al.*, 2009; Ohuegbe & Hussain, 2014).

While a study by Tudisco *et al.*, (2013) investigated the feasibility of real-time sonoelastography in the assessment of the mechanical tendon properties in small unilateral supraspinatus tears, the current study assessed the mechanical properties of asymptomatic and symptomatic tendons to establish supraspinatus strain ratio values and the diagnosis of tendinopathy. Their study described the sonoelastographic properties of torn supraspinatus tendons and correlated sonoelastography findings with clinical results and demographic data while the current study did not study torn supraspinatus tendons but the elasticity of the tendons using colour grades and strain ratio values. Their study concluded that sonoelastography was a feasible method applicable in the assessment of tendon quality in small supraspinatus tears, and its findings correlated with the clinical results of the patients.

4.4.5 Diagnostic reference standard

In the current study, the results showed lower accuracy levels of ultrasound than sonoelastography when confirming clinically diagnosed supraspinatus tendinopathy with strain ratio (65% vs 92% against 59% vs 68%). However, since the presence of potential clinical symptoms of tendinopathy mimic other shoulder pathologies like SASD bursitis, impingement and tears, the author thought that these could have lowered the accuracy results of ultrasound and sonoelastography modalities used. A careful analysis showed that Obuchowski (2003) and Lewis (2009) in their review papers upheld this opinion. However, they agreed that adoption of certain measures like choosing better reference standard and applying a statistical correction to the estimates of accuracy could have minimized these effects of symptoms that mimic presence of tendinopathy.

In his study Warden *et al.* (2007) showed ultrasound to be more accurate than MRI in confirming clinically diagnosed patellar tendinopathy. However, these results were subject to some potential biases such as imperfect standard bias, verification bias and review bias, which could have affected their accuracy, sensitivity and specificity.

Also, according to Lewis (2009), significant morbidity is involved in rotator cuff pathology due to poor and insufficient understanding of the pathoaetiology of the rotator cuff pathology as this may contribute to lack of accurate diagnosis in the assessment process. Literature review listed at least three reasons why clinical assessment methods for rotator cuff tendinopathy are unable to isolate individual tendons and other structures. The reasons include one, the inability to selectively test the individual rotator cuff tissues; two, the position and innervation of the subacromial bursa that gets stretched and compressed during clinical tests; and three, the lack of correlation between symptoms and contemporary methods of imaging (Lewis, 2009). These have led to the production of inaccurate diagnosis.

According to Clark & Harryman (1992), rotator cuff tendons do not work as separate units. In addition, clinical tests put forward to identify symptoms originating from the individual entities (a confluence of tendons, coracohumeral ligament and glenohumeral capsule) that are involved in the pathoaetiology of tendinopathy are unsubstantiated (Cyriax & Cyriax, 1982; Magee, 1997). Based on this factor, clinical tests for the rotator cuff have demonstrated lack of specificity according to Hegedus *et al.* (2008) and Miller, Forrester & Lewis, (2008). This is in line with the result of the present study that showed lower specificity of clinical diagnosis, 57% and 63% when ultrasound and sonoelastography were compared respectively. For this reason, a study proposed an alternative method referred to as 'the shoulder symptom modification procedure' for the clinical examination of the shoulder in order to improve specificity (Lewis, 2009).

The use of strain ratio in the current study to produce a good value of area under ROC curve of 0.94 is comparable to existing values from other studies. This result is comparable to results of summary ROC curves for MR arthrography,

MRI, and ultrasound for all supraspinatus tendon tears with respective values of area under the ROC curve which was greatest for MR arthrography (0.935), followed by ultrasound (0.889) and then MRI (0.878) (de Jesus *et al.*, 2009).

Currently, there are no published studies on tendon ROC curves to draw comparisons from. The few published studies on ROC curve are those of breast and thyroid and they showed comparable results (Garra, 2011; Xing *et al.*, 2011). The study by Garra (2011) showed an area under the ROC curve of 0.88 to 0.95.

The current study used strain ratio value cut-off point of 4.0 derived from the ROC curve as the standard reference point to diagnose tendinopathy. Using this value, the strain ratio measurement had 98% sensitivity and 85% specificity with area under curve of 0.94. Similarly, receiver operating characteristic curve analysis was used to compare the diagnostic performance of the strain ratio and that of conventional sonography in the study by Xing *et al.* (2011). When a cut-off point of 3.79 was used, significantly different strain ratios for benign (mean \pm SD, 2.97 ± 4.35) and malignant (11.59 ± 10.32) lesions were obtained ($p < 0.0001$). The strain ratio measurement had 97.8% sensitivity and 85.7% specificity. The area under the curve for the strain ratio was 0.92.

Using a similar approach, another study on lymph nodes that evaluated the diagnostic utility of sonoelastography in differentiating reactive and metastatic axillary lymph nodes in breast cancer revealed that sonoelastography increased the sensitivity of ultrasound in the detection of metastatic axillary lymph nodes. The study also revealed that combined ultrasound and sonoelastography showed higher sensitivity (87.1%) than ultrasound alone. With a strain ratio cut-off point of 2.3, sensitivity was 82.8%, and specificity was 56.3% (Choi *et al.*, 2011).

4.4.6 Blinding and biases – selection, measurement and analysis

The current study identified the value of ultrasound and sonoelastography as diagnostic tests for the detection and quantification of supraspinatus tendinopathy in adult population with shoulder pain. Painful shoulders in sonography practice are not uncommon problems. Reports of several authors indicate that ultrasound has proven to give valuable information when pathology

of the rotator cuff is suspected (Teefey *et al.*, 2000; Moosmayer, Heir & Smith 2007). The current study used diagnostic methodology approach, and there were identified biases in the study.

The sonoelastography results were unaffected though the operator of the sonoelastography and strain ratio was not blinded to patients' clinical history because of the autocorrelation principle of the sonoelastographic technique (Pesavento, Perrey, Krueger & Ermert, 1999). By this principle, the results of the sonoelastograms and strain ratio values were based on the ability of autocorrelation software of the scanner to distinguish tissue elasticity independent of their sonographic appearance. It is important to note that no published paper on the accuracy of sonoelastography has listed blinding as a bias in their study as it was not necessary and would have had no effect due to the inherent autocorrelation in the scanners. The outcome of the current study was completely in agreement with published techniques and protocols.

All the patients were equally exposed to ultrasound, sonoelastography and strain ratio measurement. No patient was excluded from sonoelastography because of a negative ultrasound result. The 2x2 contingency tables showed good presentation of the comparisons. The current study avoided work-up (verification) bias (Sackett & Haynes 2002a) as ultrasound findings were not used for decision-making for any intervention because of a negative ultrasound result. Work-up bias occurs when patients with negative test results are not evaluated with the reference standard test. From the methodology of the current study, the results of the test of interest (sonoelastography) were not influenced by the results of the reference standard (ultrasound and clinical diagnosis). By this the author eliminated the possibility of interpretation or review bias (Bachmann, ter Riet, Weber & Kessels, 2009, Sackett *et al.*, 2002b). This eradicated the possibility of inflated measures of diagnostic accuracy. Both tests were performed independent of each other as the sonoelastography results were based on its autocorrelation principle which could not be subjectively influenced.

During this research, the operator of ultrasound was blinded to the patients' medical history while the operator of sonoelastography and strain ration was not. This did not introduce spectrum bias because it could not have affected the

sonoelastography results which were not subjective, but completely objective due to the presence of combined autocorrelation method that provided images consistent with tissue compressibility as previously explained.

The test results of the current study did not occur by chance. Available clinical data used in the interpretation of the ultrasound, elastography and strain ratio results did not affect the estimates of test performance. This is because tissue elasticity could not be affected by that.

Confidence interval is affected by sample size and variability among subjects. The sample sizes for the asymptomatic (284) and symptomatic (204) appeared statistically normal for a quantitative study. According to Altman and Bland (1994), the confidence interval gives a measure of the precision (or uncertainty) of study results for making inferences about the population of patients with painful shoulder. The larger the sample size, the larger the number of outcome events and the greater the confidence that the true relative risk reduction is close to the value stated: the confidence intervals narrow and "precision" is increased.

Whiting *et al.* (2003) stated that the results of both the index and reference tests should be collected at the same time to prevent misclassification due to recovery or progression of the condition in order to prevent disease progression bias. This was possible in the current study as the interval between the index and reference tests was barely minutes.

However, incorporation bias was eliminated as the index result was not used to establish the final diagnosis (Whiting *et al.*, 2003) in the current study. This did not result in over-estimation of the accuracy of the study by decreasing the number of false positives and false negatives (Moons & Grobbee, 2002).

4.4.7 Limitations of the study

This study has several limitations. One limitation of this study was the impact of operator dependency errors as pressure was applied with the use of a free-hand technique. Several authors have argued that this technique might affect reproducibility (Regner *et al.*, 2006; Fleury Ede, Fleury, Piato, & Roveda, 2009). A report by Itoh *et al.* (2006) considered this as a limitation and thought that

variable interpretations are possible on the same elastographic image as image selection was done by the performer (Itoh *et al.*, 2006). It was in the light of this that cautious attempts were made to moderate the pressure exerted with the ultrasound probe. This was to overly avoid high and very low pressures because of the nonlinear properties of tissue elasticity (Itoh *et al.*, 2006; Klauser *et al.*, 2010; Srinivasan & Dubey, 2012).

Also, the shoulder has diverse slopes in different individuals which are thought to affect compressibility (Hiltawsky *et al.*, 2001). Although, there may be variability in the compression motions, an in-built colour bar in the form of a pressure indicator is seen in the middle of the screen with values between 1 and 5. In the current study, the optimized probe compression using the freehand technique gave a value of 3 on the pressure indicator. This gave the optimum colour codes for image acquisition and interpretation as seen in other studies by Cho, Moon & Park (2009) and Zhu *et al.* (2008). This guide served as standardized criteria and minimized subjective deficits in operating skills of the operators.

In this study, the near-proportional relationship between pressure exerted and tissue strain was maintained by monitoring the visual indicator scale on the machine which gives the optimal dynamic range of pressure. This is because when the pressure decreases or increases below a certain level, the pattern of the elasticity image starts to change drastically. Monitoring the visual indicator helps to decrease interobserver variability, a major limitation, and ease image acquisition. Image acquisition in the current study was best in the compression phase when best contrast images are available. This was supported by a study by Itoh *et al.* (2006). As explained previously, visual indicator between 3 and 4 on the Hitachi ultrasound machine was considered to give optimum compression for image acquisition.

Also, three compression and decompression cycles was performed for every supraspinatus tendon in this study. A similar method was used on another study on patellar tendons which performed at least three cycles for every tendon third and saved images from each cycle (Klauser, Faschingbauer & Jaschke, 2010). It is believed that sonoelastography at the start and finish of each pressure cycle fails to provide correct elastograms due to incorrect calculation of elasticity of

initial and late scans. However, the results are not affected by this artefact when the required images are obtained during compression. Multicompression imaging is used to improve the signal-to-noise ratio of sonoelastography images (Konofagou, Ophir, Kallel & Varghese, 1997; Skovoroda, Emelianov & O'Donnell, 1995).

In this study it was obvious that maintaining homogeneous probe pressure application was a limitation. Elasticity changes constantly at the border of the transducer in longitudinal scans. This could have been as a result of inhomogeneous pressure application. This effect could lead to tissue shifting due to unilateral compression which might influence elastograms at the border. This was another potential limitation. A different study divided the Achilles tendon in three thirds to allow for overlapping scans so that results of the borders of longitudinal scans were not included in the diagnostic process (De Zordo *et al.*, 2007a). However, in the present study, the supraspinatus tendon was not divided into sections and the results were based on longitudinal images. This could explain why longitudinal sections were used for the present study as tissue shifting would be more pronounced if transverse sections were used. In the patellar tendon, the use of a gel standoff pad helped to alleviate this problem (Klauser, Faschingbauer & Jaschke, 2010). However, the magnitude of the compression is argued to not overtly cause any significant shift.

The size of the region of interest used to calculate the strain ratio in the study was small, consistent and at a consistent depth within the supraspinatus tendon. This was necessary in order to acquire an elastogram of consistent characteristics for optimal strain ratio values. This methodology was consistent with a study on Achilles tendon where the authors recommended that the depth of the ROI should be three times the tendon size and width, and about three quarters of the screen for longitudinal scans (Klauser, Faschingbauer & Jaschke, 2010). According to Klauser and colleagues, the dimension of the sonoelastography window or ROI influenced elastograms as the mean of elasticity of each image pair was calculated by sonoelastography. A larger ROI that included more neighbouring soft tissue made a tendon appear 'harder' with more blue colour than a smaller ROI where less soft adjacent tissue was added. The study recommended that the ROI or box be standardized. Nonetheless,

sonoelastography in its current status is still considered a subjective technique. Both training and interpretive skills are required.

A technical limitation of sonoelastography noted in patellar tendons was that elastograms were calculated only at a distance of ≥ 1.2 mm from the probe. In slim individuals, skin-to-tendon distance was < 1.2 mm, and therefore correct elastograms were be obtained without using a gel pad, which appeared to be the best way to resolve this limitation (Klauser, Faschingbauer & Jaschke, 2010). However in the present study on supraspinatus tendon, the presence of the deltoid muscle compensated and reduced the effect of this limitation but did not completely eliminate it. This limitation can be averted by using a probe of higher frequency such as 16 to 18MHz to improve the resolution of the images and optimize accuracy.

The limitations of inter-observer and intra-observer variability in sonoelastography imaging of tendons are discussed in the next chapter. However, there are no clear cut agreements on the issue of inter-observer and intra-observer tendons. Literature evidence varies and due to the operator dependency of the technique it is yet to be certain how much impact this has (Nazarian, 2007). Image construction in sonoelastography is known to lead to certain soft-tissue artefacts as demonstrated in the current study, and corroborated by other studies on Achilles tendon and common extensor tendon as well as in surrounding bony structures (De Zordo *et al.*, 2009a; De Zordo *et al.*, 2010). However, with further practice, it was possible to differentiate the artifacts from consistent images. Also, repeating the scan three times helped to reduce this limitation.

Some other factors that affect elastography include patient factor (size of shoulder/SST thickness) and acquisition process factors (e.g., the type of ultrasound elastography device, extent of tissue compression, and performer variability), and interpretation variability (Itoh *et al.*, 2006; Thomas *et al.*, 2006; Yoon *et al.*, 2011). The present research did not assess these. The assumption was that variability in this research may have been due to differences in image acquisition and variable interpretation during the freehand technique. Although, there was variability in the compression motions, an in-built colour bar in the form

of a pressure indicator in the middle of the screen helped to moderate compression force to provide optimum colour codes for image acquisition and interpretation (Cho, Moon & Park, 2009; Zhu *et al.*, 2008).

A high strain ratio value of 52 and low value of 1.9 were recorded in the current study and this was seen as a limitation of sonoelastography technique. The high values were seen in cases of calcific tendinopathy. This finding was also corroborated in the study by Yerli, Yilmaz, Kaskati & Gulay (2011) where the authors revealed high values in their study. However, obvious supraspinatus tendinopathy showed smaller values in the range of 1 to 4 in the current study. The high value recorded in calcific tendinopathy reflected the high atomic number seen in calcium as compared to softer tendons that have lower atomic number as a result of their high water content. Two studies by Cluett (2008) and Rechartt *et al.* (2010) discoursed that calcific tendinitis might be age-related and occurred in individuals between the ages of 30 to 40, and was more common in diabetics. However, the patients recorded in this study were not diabetic.

A study by Yerli, Yilmaz, Kaskati & Gulay (2011) stated that it took longer to conclude the examination due to additional calculation and time after the elasticity map was obtained. However, in the present study, the additional investigation time was not significant but minor in view of the diagnostic benefits of SE. The use of strain ratio measurements increased the accuracy of detection of tendinopathy in this study.

Like most applications, real-time sonoelastographic imaging limitations can be overcome by better quantification tool (e.g. strain ratio, histogram analysis, use of higher examination frequencies (current study used maximum 13MHz; initial studies used maximum 10MHz), and use of broadband transducers (Ciurea *et al.*, 2011).

SE provides additional information that would help broaden its use in musculoskeletal imaging. This, however, would depend on enhancing the capability to interpret sonoelastographic artefacts and taking advantage of the information it provides (Klauser, Faschingbauer & Jaschke, 2010).

Chapter 5 – Phase 3 Study

Intra-observer and inter-observer variability & reliability

5.1 Introduction

This chapter presents a report of the Phase 3 of the research. This phase evaluated intra-observer and inter-observer variability and reproducibility in normal “asymptomatic” supraspinatus tendons using two different groups of normal volunteers referred to as Group 1 and Group 2. The author and two other musculoskeletal sonographers with five years’ experience of sonoelastography undertook this phase of this research. The author is identified as Observer 1. The other two independent musculoskeletal sonographers are referred to and identified as Observer 2 and Observer 3.

5.2 Methods for Phase 3 Study

5.2.1 Protocol for intra-observer and inter-observer variability

The supraspinatus tendons were examined using the same protocol for scanning the tendons used in Phase 1 and Phase 2. For Group 1, 50 supraspinatus tendons were examined by Observers 1 and 2. For Group 2, 40 supraspinatus tendons were examined by Observers 1 and 3. These 40 supraspinatus tendons were recruited from the same study population used in Phase 1. Two measurements of the strain ratio were made on each tendon when assessing intra-observer reliability. Real-time sonoelastography images with their strain ratio measurements were obtained and independently analysed. Each tendon was examined two times in longitudinal sections and the ratio between the deltoid muscle and the tendon strain (strain ratio) was calculated and recorded for each tendon. The intra-observer and inter-observer agreement and reproducibility of the strain values were compared.

5.2.2 Data analysis

For each group, a chi-square test for independence was used to ascertain if there was any association between gender and tendon grades. To find out if there was a significant difference in age between the two groups, an independent-samples *t-test* was conducted.

The intra-observer and inter-observer agreement and reproducibility of the strain values were assessed using the *kappa* statistics.

The intra-observer agreement was calculated with inter-rater agreement using the intraclass correlation coefficient (ICC). For intra-observer variability, the first SR values were compared with the second SR values with the same settings on the ultrasound machine and probe frequency using the *kappa* statistic. All results were reported at a significance level of $p < 0.001$. (A p -value of less than 0.001 was considered to be statistically significant). The ICC described the variation of the repeated measurements by the same observer.

The inter-observer variability was calculated with the inter-rater agreement using *kappa* between Observer 1 and Observer 2. The individual strain ratio values and colour grades were regarded as an entity and assigned a value of either Grade 1 or Grade 2, and these grading scores were used by each observer as the overall score for each measurement. The scores for Observer 1 were compared with the scores for Observer 2 using the *kappa* statistic. The same was done for measurements for Observer 1 and Observer 3.

The *kappa* statistic considered the null hypothesis of no agreement against the alternative hypothesis of agreement further than what would be expected by chance. *Kappa* statistic value of 0 indicates agreement that is expected to be due to chance and a *kappa* statistic of 1 indicates complete agreement.

The same statistical analysis was carried out for both groups. All statistical parameters were calculated using the Statistical Package SPSS 20.0 (SPSS Inc., Chicago, Ill., USA).

5.3 Results

5.3.1 Group 1 – variability between Observers 1 and 2

There were 26 males (52%) and 24 females (48%) shoulders in the sample giving a total of 50 participants. The age range was between 20 and 45 with a

mean of 30.1 and a standard deviation of ± 5.5 . The colour grading patterns that were demonstrated by the supraspinatus tendon elastograms were consistent with the consecutive images and sonograms.

Using chi-square test for independence, the association between gender and tendon grades was assessed. Using continuity correction, the Pearson chi-square value was 0.69, with an associated significant value of 0.41 (larger than the alpha value of 0.05). This implies that this outcome is not significant. This means that there is no association between gender and tendon grade or group. The phi coefficient value was 0.16 and is considered medium effect using Cohen's criteria (1988). (The values for Cohen's criteria are 0.10 for small effect; 0.30 for medium effect; and 0.50 for large effect). In summary, a chi-square test for independence (with Yates Continuity Correction) indicated no significant association between gender and tendon grades, $X^2(1, n = 50) = 0.69, p = 0.41, phi = 0.16$.

To find out if there is a significant difference in age between the two groups, an independent-samples *t-test* was conducted. This type of *t-test* was used in order to compare the mean scores of tendon grades for two different groups. There was no statistically significant difference in values for males ($M = 1.38, SD = 0.50$) and females ($M = 1.54, SD = 0.51$); $t(48) = 1.10, p = 0.16$ (two-tailed).

5.3.2 Results for intra-observer agreement

The intra-observer agreement for Observer 1 using the intraclass correlation coefficient (ICC) was calculated to be 0.886 and the value showed a considerable level of agreement with a significance of $p < 0.0005$. The Cronbach's Alpha, which is another measure of reliability, agreed with the ICC about the high level of reliability between the two measures. The Cronbach's value was 0.939 (a value of 0.70 and above is considered reliable). The intra-observer agreement using the ICC was also calculated for Observer 2 and the value was 0.913. This value showed a considerable amount of agreement. The Cronbach's Alpha value was 0.954 and considered reliable. The results for intra-observer analysis are shown in Table 5.1 and the table of reference value is shown in Table 5.2.

Table 5.1: Results for intra-observer analysis.

Observers	ICC (<i>k</i> - statistic)	Cronbach's Alpha	<i>P</i> – value
Observer 1	0.886	0.939	< 0.001
Observer 2	0.913	0.954	< 0.001

Table 5.2: Table for *Kappa* values and strength of agreement (Peat, 2001).

Strength of Agreement	Moderate	Good	Very Good
<i>Kappa (k)</i>	0.5	> 0.7	> 0.8

5.3.3 Results for inter-observer agreement

The overall grading scores were used for the comparisons, and there was good inter-rater agreement beyond that expected to have occurred by chance between observer 1 and observer 2. The value for *kappa* in this case was 0.715, and all results were reported at a significance level of $p < 0.001$ (Table 5.3). From the result, observers 1 and 2 had positive agreement in 25 (50%) tendons and negative agreement in 18 (36%) tendons. Thus, there was an overall agreement of 86% and disagreement of 14%.

Table 5.3: Table for *kappa* values and strength of agreement (Landis and Koch, 1977).

Strength of Agreement	Poor	Fair	Moderate	Good	Very Good
<i>Kappa (k)</i>	< 0.20	0.21–0.40	0.41–0.60	0.61–0.80	0.81–1.00

5.3.4 Group 2 – variability between Observers 1 and 3

There were 22 males (55%) and 18 females (45%) shoulders in the sample giving a total of 40 participants. The age range was between 24 and 54 with a mean of 32.4 and a standard deviation of ± 4.9 . The colour grading patterns that were demonstrated by the SST elastograms were consistent with the consecutive images and sonograms.

Using chi-square test for independence, the association between gender and tendon groups was ascertained. Using continuity correction, the Pearson chi-square value is 1.21, with an associated significant value of 0.27 (larger than the alpha value of 0.05) indicating that this result is not significant. This means that there is no association between gender and tendon group. The phi coefficient value of 0.20 is considered medium effect using Cohen's criteria (1988) (0.10 for small effect; 0.30 for medium effect; and 0.50 for large effect).

In summary, a chi-square test for independence (with Yates Continuity Correction) indicated no significant association between gender and tendon grades, $\chi^2(1, n = 40) = 1.21, p = 0.27, \phi = 0.20$.

To find out whether there is a significant difference in age between the two groups, an independent-samples *t*-test was conducted. There was not a statistically significant difference in values for males ($M = 1.31, SD = 0.47$) and females ($M = 1.50, SD = 0.51$); $t(48) = 1.39, p = 0.19$ (two-tailed).

5.3.5 Results for intra-observer agreement

The intra-observer agreement for Observer 1 using the intraclass correlation coefficient (ICC) was calculated to be 0.875 and the value showed a considerable level of agreement with a significance of $p < 0.0005$. The Cronbach's Alpha was 0.932.

The intra-observer agreement using the ICC was also calculated for Observer 3 and the value was 0.922. This value showed a considerable amount of agreement. The Cronbach's Alpha value was 0.959.

The results for intra-observer analysis are shown in Table 5.4 and the table of reference value is shown in Table 5.3.

Table 5.4: Results for intra-observer analysis.

Observers	ICC (<i>k</i> - statistic)	Cronbach's Alpha	<i>p</i> - value
Observer 1	0.875	0.932	< 0.001
Observer 3	0.922	0.959	< 0.001

5.3.6 Results for inter-observer agreement

The overall grading scores were used for the comparisons, and there was good inter-rater agreement beyond that expected to have occurred by chance between Observer 1 and Observer 3. The value for *kappa* in this case was 0.750, and all results were reported at a significance level of $p < 0.001$ (Table 5.4). From the result, Observers 1 and 3 had positive agreement in 19 (47.5%) tendons and negative agreement in 16 (40%) tendons. Thus, there was an overall agreement of 87.5% and disagreement of 12.5%.

5.3.7 Summary of *kappa* values

Table 5.5 compares the *kappa* values for the intra-observer agreement using the intraclass correlation coefficient for Observers 1 and 2 in Group 1 and Observer 1 and 3 in Group 2. The values are comparable and demonstrate very good level of agreement within each observer.

Comparison between the inter-rater agreements between the two groups showed *kappa* values of 0.715 (Group 1) and 0.750 (Group 2) which demonstrate good and comparable agreements (Landis and Koch, 1977). This shows that intra-observer and inter-observer agreements of sonoelastography are good and reproducible indicating good reliability.

Table 5.5: Table for comparison of *kappa* values of intra-observer agreement between the two groups.

	Intra-observer agreement ICC		
	Group 1	Group 2	
Observer 1	0.866	0.875	Observer 1
Observer 2	0.913	0.922	Observer 3

5.3.8 Summary of findings

The *kappa* values for the intra-observer agreement using the intraclass correlation coefficient for observers 1 and 2 in Group 1 and observer 1 and 3 in Group 2 showed very good level of agreement within each observer.

Comparison of the inter-rater agreements between the two groups showed *kappa* values of 0.715 (Group 1) and 0.750 (Group 2) which demonstrated good and comparable agreements. This shows that intra-observer and inter-observer agreements of sonoelastography are good and reproducible.

5.4 Discussion

In the study, the intra-observer agreement in both groups 1 and 2 was classified as very good using the intraclass correlation coefficient (ICC). The ICC value was 0.89 for observer 1 and 0.91 for observer 2 in group 1, and 0.88 for observer 1 and 0.92 for observer 3 in group 2. The inter-observer *kappa* value for this study was 0.72 for study 1 and 0.75 for study 2 at a significance level of $p < 0.001$. The results of this study are similar and comparable to the results of another study by Drakonaki, Allen & Wilson, (2009) that used a similar technique, system setting and transducer; their results showed intra-observer CC of 0.88 and inter-observer CC of 0.84 on the sonoelastographic study of the Achilles tendon (Drakonaki, Allen & Wilson, 2009). Their study reviewed the colour grades of sonoelastograms and evaluated the reproducibility of the strain index. It is clear that their study had a better inter-observer result than the present study (0.84 versus 0.72/0.75) but slightly lower intra-observer result than the present study (0.88 versus 0.89/0.91).

In a different study, Havre *et al.* (2008) used phantoms and a visual analogue scale with different system settings and transducers. The results of their study produced satisfactory but lower intra-observer and inter-observer agreement with *kappa* values of 0.67–0.75 and 0.55–0.56 respectively, using the categorical scale. The difference between this study and the present study is that a tissue-mimicking phantom was used instead of normal tissue. Also, their study used different system settings and transducer while the current study used consistent and same machine settings. It is uncertain if the results of their study could be succinctly applied to verify intra-observer and inter-observer agreement in view of these differences.

In contrast, other studies by Janssen, Dietrich, Will & Greiner, (2007) and Fraquelli *et al.* (2007b) reviewed qualitative appearances of images but did not evaluate the reproducibility of the strain indices. A study of endoscopic real-time elastography by Janssen, Dietrich, Will & Greiner (2007) examined lymph nodes and reported an inter-observer *kappa* value of 0.84. This result is comparable to the result of the present study, but could have different implications as its intracavitary environment is different from that of the present study. A study of transient elastography for liver fibrosis by Fraquelli *et al.* (2007b) reported inter-CC of 0.98 as shown in Table 5.7.

Table 5.6: Intra-observer *k*-value comparison with other studies.

Intra-CC (Drakonaki & co)	0.88
Intra-CC (Havre <i>et al.</i> - Phantom)	0.67-0.75
Intra-CC (Yoon <i>et al.</i>)	0.46
Intra-CC Group 1 (Ohuegbe)	0.72
Intra-CC Group 2 (Ohuegbe)	0.75

Itoh *et al.* (2006) in their study on the clinical application of sonoelastography on breast disease remarked that variable interpretations could be given on the same elastographic images by different performers as images were individually selected. In line with this opinion, other studies have presented inter-observer variability as a limitation in breast elastography studies (Regner *et al.*, 2006; Fleury Ede, Fleury, Piato & Roveda, 2009). In the evaluation of inter-observer variability of elastography on real-time ultrasound and how it influenced the agreement of final assessment on ultrasound, Yoon *et al.* (2011) agreed that elastography improved the specificity, positive predictive value, and accuracy of ultrasound. However, their study noted that significant inter-observer variability existed ($k = 0.25$), with real-time elastographic performance showing fair agreement ($k = 0.46$) as shown in Table 5.6 and Table 5.7.

Table 5.7: Inter-observer *k*-value comparison with other studies.

Inter-CC (Drakonaki & co)	0.84
Inter-CC (Havre <i>et al.</i> -Phantom)	0.55-0.56
Inter-CC (Fraquelli <i>et al.</i>)	0.98
Inter-CC (Janssen <i>et al.</i>)	0.84
Inter-CC Group 1 (Ohuegbe)	0.72
Inter-CC Group 2 (Ohuegbe)	0.75
Inter-CC (Yoon <i>et al.</i>)	0.25

On a positive note, studies demonstrated results with fair to moderate inter-observer agreement using tissue-mimicking phantom (Havre *et al.*, 2008), and normal tissues (Abdullah, Mesurolle, El-Khoury & Kao, 2009).

The unique thing about the current study is that it compared the effect of intra-observer and inter-observer agreement and variability in two different sets of groups of normal supraspinatus tendons. The reason was to further compare inter-rater agreement in two groups. The result showed good and comparable agreement with *kappa* values of 0.72 (for isolated healthy volunteers) and 0.75 (from Phase 1 healthy volunteers). This suggests that the intra-observer and inter-observer reliability results of the current study can be used as a reliable clinical parameter. Since this showed that sonoelastography is reproducible, further studies of intra-observer and inter-observer variability on supraspinatus tendinopathy would be more suitable for clinical conditions (Hiltawsky *et al.*, 2001; Abdullah, Mesurolle, El-Khoury & Kao, 2009).

Using the concept of visual resolution which is defined as the amount of detail that can be distinguished in an image by the human eye, the intra-observer and inter-observer variability can be associated with the difference in perception in different observers. Sonoelastograms stand out and appear different because there is colour on the image which is easily differentiated by the eye. Two factors are implicated here: first, the psychomotor skills of the operator that are variable. The psychomotor skill is affected by the cognitive calculating skills of achieving the right compressions with the probe movement where the operator spends less time with perfecting the movement skills of the freehand technique. It is also affected by the autonomic stage where the operator refines his skill through practice. Second, the operator's observation skill which is affected by the amount of detail that the operator's eye can distinguish equally and this is variable. These two skills in synergy can be used to explain the differences in perception in individuals that relate to operator dependency; this can be used to explain intra-observer and inter-observer variability.

In literature review in Chapter 2, it was mentioned that reproducibility was reported to be influenced by the operator's experience according to Sporeal, Sirli, Popescu & Danilă, (2011). The above theory of visual resolution and

associated psychomotor and observation skills could have contributed. Whether this may have been the reason for a lower value of 0.25 in the study by Yoon *et al.* (2011), remains to be seen as their study showed significant inter-observer variability.

A recent paper showed excellent interobserver reliability of sonoelastography when comparing sonoelastography of the supraspinatus tendon with conventional ultrasonography and magnetic resonance imaging (Seo, Yoo and Ryu, 2014). The result showed “almost perfect agreement” with a weighted kappa coefficient of 0.83. This result corroborates the findings of this research. However, the results of their study were based on colour grading while the result of this study was based on quantitative measurements of strain ratio.

The next chapter summarizes the research work and proffers recommendations with suggestions of areas of further research.

Chapter 6 Conclusion

6.1 Introduction

This chapter presents the concluding arguments and significance of this study with its implications for practice. It presents a review of the study objectives with outcomes of each phase of this research. The chapter examines how this study's findings fits with relevant areas of sonoelastography imaging in soft tissues like the breast, thyroid and other musculoskeletal imaging. It concludes by highlighting areas of further research and plans for dissemination of the findings of this study.

6.2 Implications of this research findings and change in practice

One of the rationales of this study was to assess the impact of sonoelastography on improving the accuracy of detection of supraspinatus tendinopathy since the supraspinatus tendon is the most frequently affected tendon of the rotator cuff tendons in patients with shoulder pain. The result of this study indicated increased accuracy and early diagnosis of supraspinatus tendinopathy using sonoelastography than ultrasound. The study measured and provided increased accuracy of tendinopathy detection quantitatively by measuring the strain ratio. This result is reproducible and reliable, and can be applied to this group of people to provide an early diagnosis. This result defines the management pathway for the patient, and will in turn lead to early treatment which indicatively will minimise absence from work from sick leave (Herring & Nilson, 1987; Jones, Britain & Britain, 1998; Linsell *et al.*, 2006). This is expected to impact positively on the health economy (Linsell *et al.*, 2006; Matsudaira, Hara, Arisaka & Isomura, 2010).

The sonoelastographic technique has the potential to lead to earlier intervention, better patient management and quicker follow-up examinations. This is because the results are displayed as quantitative figures (strain ratio) which give definitive results. This technique is reproducible and can be taken into practice anywhere. The values of the result could help decide what to do with the patient and

influence the treatment pathways that may be relevant. Srinivasan & Dubey (2012) sum up the value of this promising imaging technique called sonoelastography and predicted that:

“the clinical value of sonoelastography of the supraspinatus tendon will only be validated if it is able to offer a substantial advantage in the diagnosis of lesions with poor or indeterminate imaging features (on grey scale US and MR imaging) such as tendinosis where a softening, if reliably detected early will be of clinical significance in the management”.

This prediction was achieved in this study. The results obtained in this study have made a case for sonoelastography to be used in the diagnosis or as an adjunct for the diagnosis of supraspinatus tendinopathy.

The outcome of this study has demonstrated that sonoelastography can define tissue changes earlier in damaged tendons leading to early and more definitive diagnosis. Two result groups, normal and abnormal, were demonstrated in this study. In the abnormal group, two sonoelastographic grades were shown - tendons with yellow colour and tendons with red colour present. The tendons with yellow and red colourations demonstrated values less than 4.0 on strain ratio scale. This would in turn suggest altering the patient's treatment pathway because of the very definitive quantitative result. The aim is to initiate early rehabilitation before inflammation and tendon degeneration commence. The finding of 9.9% softened tendons in normal volunteers can be used to emphasize the importance of previous studies that showed that imaging appearances do not particularly reflect clinical symptoms and diagnosis, as these colour changes were seen in asymptomatics (Peers & Lysens, 2005; Richards, Win & Jones, 2005). This becomes important in deciding the management pathway for such 'patients'. Fredberg *et al.* (2004) suggested the solution that tendon load could be reduced before tendinopathic symptoms became evident, and treatment to be commenced before the condition became chronic.

The results of this study will influence practice positively by being used in clinical settings for the interpretation of sports injuries, orthopaedic diseases and evaluation of the repair process. The application of colour grades and

quantitative values during investigations will facilitate this. This is expected to reduce patient recovery time and improve quality of life, and subsequently improve services and reduce cost (Linsell *et al.*, 2006; Matsudaira, Hara, Arisaka & Isomura, 2010; Rees, Wilson & Wolman, 2006).

Table 6.1: Summary of achieved objectives.

Objectives	Description
01	To conduct comprehensive and critical reviews of literature to ascertain the efficacy of previous studies using sonoelastography.
01 Achieved	This has been achieved in literature review in chapter 2.
02	To establish sample groups of supraspinatus tendons of normal adult volunteers referred to as “the asymptomatic group” and patients with clinical signs of supraspinatus tendinopathy referred to as “the symptomatic group” and establish baseline strain ratio measurements and estimate diagnostic accuracy.
02 Achieved	The mean strain for normal supraspinatus tendons was 5.6 (± 1.24 SD); males = 5.7 (± 1.44 SD) and females = 5.4 (± 0.92 SD). There was statistically significant difference in the mean strain ratio values for males and females. Also 80.4% of tendons showed Grade 1 pattern (hard tissue) and 19.6% showed Grade 2 (mild softening). In patients with positive results for tendinopathy, the mean strain value was low measuring 3.59 (± 5.16 SD). Using CD and SR as reference standards, SE showed higher accuracy than US (65% vs 59%) and (92% vs 68%) respectively (See table 4.16).
03	To compare the diagnostic accuracy of grey-scale ultrasound and sonoelastography in the assessment of tendinopathy using clinical diagnosis and strain ratio as reference standards, and also establish a new reference standard in the form strain ratio.
03 Achieved	See Table 4.16 for tabulation of all results. SE achieved the highest sensitivity of 98%, specificity of 88% and accuracy of 92% ($p < 0.001$). A ROC curve cut-off value of 4.0 on SR was used as a reference standard to indicate presence of pathology.
04	To assess the intra-observer and inter-observer variability and reproducibility in normal “asymptomatic” supraspinatus tendons.
04 Achieved	The <i>kappa</i> values for the intra-observer agreement showed very good level of agreement within each observer. Comparison of the inter-rater agreements between the two groups showed <i>kappa</i> values of 0.715 (Group 1) and 0.750 (Group 2) which demonstrated good and comparable agreements.

The study has proposed a new reference standard called strain ratio for the diagnosis of supraspinatus tendinopathy. This parameter has emphasized sonoelastographic changes that are present in the supraspinatus tendon which define clinical and subclinical processes that are not evident on ultrasound.

When combined with grey-scale ultrasound, sonoelastography improved imaging accuracy of tendinopathy. This will forestall repeat examinations due to definitive diagnosis and consequently reduce patient waiting time and emotional burden. Sonoelastography will be useful for distinguishing asymptomatic but sub-clinical tendinopathy from normal grey scale ultrasound. These findings will preclude the need for a repeat ultrasound scan or second opinion scans due to indeterminate results leading to change of practice in diagnosing supraspinatus tendinopathy.

These are all noted in the summary of achieved objectives as shown in Table 6.1.

6.3 Study contribution

1. The study findings support the study theory that sonoelastography is effective in the assessment of tendinopathy of the supraspinatus tendon in patients with shoulder pain. The outcomes of this study show that supraspinatus tendons demonstrate three elastographic colour grading patterns to ascertain the presence or absence of pathology:

- Grade 1 pattern shows a characteristic blue-green pattern which is an indication of hard tissue appearance and normal tendon. The mixture of green / blue colouration varies from subject to subject and can be predominantly blue and less of green colour.
- Grade 2 pattern shows evidence of yellow colouration within the tendon, an indication of mild tendon softening.
- Grade 3 pattern shows evidence of red colouration within the tendon. The presence of grades 2 and 3 patterns are consistent with tissue softening or tendon pathology.

2. The study has proved that strain ratio, a component of sonoelastography, is useful in measuring supraspinatus tendon elasticity. The study established the value of 5.6 ($\pm 1.24SD$) as the mean strain for normal supraspinatus tendons, while the mean strain ratio for males and females were ($5.7 \pm 1.44SD$) and ($5.4 \pm 0.92SD$) respectively. There was statistically significant difference in the mean strain ratio values for males and females. These values can be used as baseline values for further studies.

3. The study identified softening in tendons considered to be normal on grey-scale ultrasound. This softening was seen in 9.9% of the studied population and was not demonstrated on conventional ultrasound in healthy volunteers. The significance of this finding was that it can be used to emphasize the importance of sonoelastography in showing that imaging appearances did not particularly reflect clinical symptoms and diagnosis. The results indicate that these normal tendons have underlying pathology. Follow-up ultrasound on these cases was recommended during the study.

4. Strain ratio was another parameter that was identified that can now be used to assess tendon pathology. Strain ratio is not invasive, expensive and time consuming. This is the first study on sonoelastography to use it to assess tendinopathy in supraspinatus tendinopathy. This study proposed a mean strain ratio value for normal and abnormal supraspinatus tendon. The study indicated a ROC curve cut-off value of 4.0 as a reference standard to infer supraspinatus tendinopathy. Therefore, subjects would be categorized as either positive or negative for tendinopathy if their strain ratio was less or more than cut-off value of 4.0. The study substantiated strain ratio to be more accurate reference standard than ultrasound and clinical diagnosis in the assessment of supraspinatus tendinopathy. This result demonstrated that strain ratio is reliable and practical. However, since there is no better 'gold standard', it is impossible at present to prove that it is more accurate. Further longitudinal follow-up studies and multicentre studies would be necessary to establish the reliability of strain ratio as the reference standard.

5. This strain ratio results and colour grades in this study are postulated to be useful in differentiating tendinosis and tendinopathy. Tendons with 'yellow' colour indicate mild tendon softening and early changes that suggest the presence of 'tendinosis' which has been used to describe a histopathological state of degenerative tendon without any inflammatory signs or correlation with clinical symptoms. Tendons with 'red' colour indicate proper softening and more prolonged changes that suggest 'tendinopathy' which has been used for the clinical diagnosis of pain accompanied by impaired performance, and

occasionally swelling in the tendon. These findings were discussed in the literature review in chapter two (2.2.1). In this vein, sonoelastography could be used as a screening test for early or subclinical and severe supraspinatus tendinopathy.

6. In conclusion, real-time sonoelastography can be used to differentiate between healthy and symptomatic diseased supraspinatus tendons; it shows good correlation with ultrasound and clinical diagnosis findings. Sonoelastography can also be a diagnostic adjunct to conventional ultrasound in a thorough, accurate, and sensitive combined diagnostic approach when supraspinatus tendinopathy is suspected. Also, strain ratio values would provide a quantitative value to a pathologic lesion within the tendon and can be considered in the light of its inherent advantages to be a new reference standard, among others, in assessing diagnostic accuracy of tendinopathy.

6.4 Current Issues and Recommendations

The author wishes to recommend that the study findings be put to use in three ways.

- This work may be consulted as a resource material which has contributed to the body of knowledge in the emerging area of musculoskeletal sonoelastography.
- It can also be used as an adjunct with a view to aiding diagnosis of and early detection of tendinopathy and leading to improved accuracy.
- Other researchers who desire to explore the histological correlation and long-term clinical follow-up of supraspinatus tendinopathy may find this piece of work relevant. This is because it has explored both asymptomatic healthy supraspinatus tendons as well as those clinically diagnosed to be symptomatic.

From this study another reference standard, strain ratio, has been proposed which professes to have noticeable advantages. Sonoelastography was shown to be a tool that adds quantitative values in the diagnosis of tendinopathy without increasing scanning time. It helps to improve the diagnostic accuracy.

Sonoelastography is recommended as an important and useful addition to triage that will reduce cost and patient waiting time.

The art of mastering the technique of sonoelastography is a challenge of MSK ultrasound. This art requires learning time to achieve the mastery. Freehand technique is still questioned in some quarters. However, this study showed it is reproducible as over 90% of publications on sonoelastography used freehand technique. Reproducibility is influenced by the operator's experience (Sporeal, Sirli, Popescu & Danilă, 2011), but the current study shows that intra-observer and inter-observer agreements are good and reproducible. It is also important to recognize the limitations of MSK ultrasound and make appropriate referrals when necessary.

In our centre where this study was carried out, sonoelastography has been incorporated in the diagnostic work-up in imaging of tendons as an adjunct technique to grey-scale ultrasound. This action was taken to improve the accuracy of grey-scale ultrasound findings. Sonoelastography technique including strain ratio is therefore recommended to be used in addition to grey-scale ultrasound in imaging tendons.

6.5 Future Studies

The results of this study have shown some significant findings that are considerable enough to warrant further research into the sonoelastography of tendinopathy and tendon injuries. The following areas are of interest in continuing this research:

1. As this is the first study to fully investigate asymptomatic and symptomatic supraspinatus tendons, further multi-centre studies using strain ratio as reference standard would help to ascertain the clinical relevance of this parameter in suspected cases of supraspinatus tendinopathy.
2. This study could be useful in differentiating tendinosis and tendinopathy with regard to the different colour manifestations in sonoelastography. Tendons with 'yellow' colour suggest the presence of 'tendinosis' and tendons with 'red' colour suggest 'tendinopathy'. This study may not prove

it yet, but the results are pointing in this direction and therefore would require further research.

3. Further studies with long-term clinical follow-up are necessary to evaluate the accuracy of sonoelastography in detecting tendinopathy.
4. Treatment of supraspinatus tendinopathy and correlation with imaging finding could be better monitored and studied using sonoelastography and strain ratio.
5. Also, there is need to investigate the accuracy of strain ratio in weak or thin deltoid muscle of patients.
6. Repeat study with a machine of higher frequency such as 15–18MHz instead of 13MHz as used in the study.
7. This study assessed intra-observer and inter-observer variability in normal supraspinatus tendons. Further studies on tendons with pathologic changes are needed to ascertain any changes in these measurable parameters.

6.6 Dissemination

The findings of this study are expected to produce four papers which will be submitted to leading peer reviewed imaging journals such as Ultrasound, British Journal of Radiology and Radiology. The four papers include

- (a) baseline sonoelastographic and strain ratio findings in normal, asymptomatic supraspinatus tendons – there are no prior published values at the moment;
- (b) comparison of accuracy of ultrasound and sonoelastography in the diagnosis of supraspinatus tendinopathy;
- (c) the emergence of a new reference standard in establishing supraspinatus tendinopathy;
- (d) intra-observer and inter-observer reliability.

These would permit the findings of this study to influence the existing methods of identifying tendinopathies in the shoulder, and change in practice.

The findings of this research have been presented at the 45th British Medical Ultrasound Society (BMUS) Conference, Gateshead on 11th December, 2013.

The findings have also been accepted for presentation at the next 46th British Medical Ultrasound Society (BMUS) Conference holding in Manchester on the 11th of December, 2014.

The findings are to be presented to Radiography / Ultrasound Imaging students of University of Portsmouth.

The next chapter discusses the reflection on the professional doctorate programme.

Chapter 7 - Reflections on Professional Doctorate

...reflection should focus on “converting a work experience with some learning into a learning experience about work” (Glen, Clarke & Nicol 1995, p66)

7.1 Introduction

This chapter presents an account of my reflections and learning experience in this professional doctorate programme. The gains from the different ‘learning theories’ that were taught and the research methodologies considered which formed the basis of this thesis have also been presented in this chapter. It concludes with an insight into how writing this thesis has affected and reflected on my personal development and future aspirations.

7.2 Reflection on learning

I maximised my learning through critical reflection. This required that I regularly located myself in environments where I was able to access and assess different taught and research modules that were debated in the course of this training. Various theories such as those which focused on reflective practice, learning cycles and action learning helped to shape my person as I matured in this programme.

While I considered Kolb’s (1984, 1994) experiential learning cycle with associated learning styles of Honey & Mumford (1986), I was able to see how experience can be translated through reflection into concepts. These in turn were used as guidance for active experimentation and the choice of new experiences. Johns & Watson (2000) beautifully summarise this reflection in this way: ‘a window through which the practitioner can view and focus self within the context of her own lived experiences in ways that enable her to confront, understand and work toward resolving the contradictions within her practice between what is desirable and actual practice’ (p.34).

I have learnt to take initiatives on my own and work hard to accomplish the goals

I have set for myself. The ability to do this helped me to take responsibility for my self-directed learning. I realised that this made one learn more and not be too reliant on expert guidance alone. This was made possible as I reflected on the submission of Glen and colleagues (1995). They submitted that personal reflection should focus on “converting a work experience with some learning into a learning experience about work” (p.66). This was demonstrated in the length and breadth of my performance in clinical practice and training in this professional doctorate programme.

7.3 In retrospect

I had a personal desire to accomplish a life goal especially in the form of completing an acceptable research project beyond what I had done in the previous two separate Master’s degree programmes. My belief was that it would be an accomplishment which I knew would require discipline and character. This would be an accomplishment that will always be evergreen in my memory. In all ways, it has attested to be true. My personal desire is to continue to seek ways to improve diagnostic accuracy, and publishing the results based on pragmatic, clinical and empirical proofs.

7.4 Critical reflection on learning during the professional doctorate course

I had a very good learning experience during my professional doctorate programme in the University of Portsmouth Professional Doctorate course. This is reflected in the learning outcomes in the account below.

7.4.1 Part 1- learning outcomes of taught modules

In the first eighteen months of the Part 1 period of my Professional Doctorate programme, I was made to undergo what may be referred to as ‘action learning’. According to Boshyk & Dilworth (2010), action learning encompasses an approach based on learning from and with each other through discriminating questioning, fresh experience and reflective insight. Authors McGill and Beaty (1995) agree with this definition by describing action learning as ‘a continuous process of learning and reflection, supported by colleagues, with an intention of

getting things done. Through action learning individuals learn with and from each other by working on real problems and reflecting on their own experiences. The process helps to take an active stance towards life and helps to overcome the tendency to think, feel and be passive towards the pressures of life.' (p. 11). Dunn (2002) agreed with this assertion. The professional doctorate inculcated team spirit, professional development and a practice which involved working with solvable problems that yield to logic and applied knowledge leading to experiential learning (Bines 1992).

Reflective practice is more than thoughtful practice, and it is that form of practice which seeks to present situations of professional performance so that they become potential learning situations for me who continued to learn, grow and develop in practice (Jarvis, Holford & Griffin, 2003).

7.4.2 Experiential learning

Experiential learning (learning from experience) is one of the aims of critical reflection. The essence of the professional doctorate was to make me well grounded in the skills to maximise my learning both as a student and a professional (Tate & Sills, 2004). I gained knowledge in logical and coherent structure and style, ability to engage in academic debate, and competent use of appropriate media, language and relevant current literature (Dewey, 1933; Dewey, 1938). This was evidenced in national conference presentations (Ohuegbe & Ehiwe, 2011a; Ohuegbe & Ehiwe, 2011b). I developed professional artistry through the use of critical reflection, and Benner (1984) identified this as a characteristic skill of an expert sonographer who is adept to critical reflection. This artistry resulted from a marriage of '*knowing that*' (facts or scientific) and '*knowing how*' (individual experience) which was required to become a practitioner. In my journey this was evidenced in the few publications achieved so far (Ohuegbe & Ehiwe 2010a, Ohuegbe & Ehiwe, 2010b, Ohuegbe *et al.*, 2010c, Ohuegbe *et al.*, 2009a) where there was a synergy of clinical knowledge (knowing how) and recorded cases of patients (knowing that). Both were needed to produce the articles. This process required the development of awareness of personal unconsciously held beliefs and values, often referred to as tacit

knowledge.

7.4.3 The reflective practitioner

At the centre of all was the reflective practitioner, me, who derived knowledge from three basic sources: propositional knowledge (generated through research and history), personal knowledge (generated through life experiences) and practice knowledge (generated through professional experiences). On reflection, I used documentary and literature evidences which involved critical thinking and writing. As part of the evidence required, I (reflective practitioner) used experiential learning to combat the learning needs that arose in putting up articles, for instance. The intended outcome was to meet the learning needs and make changes that would improve practice. In other words, I was attempting to transform knowledge (propositional and experiential) into practice change by reflecting on it and critically evaluating the experiential knowledge and bring it to the fore (Moon, 2002).

Having successfully completed the previous modules, I was well equipped and bold to critically analyze the philosophical assumptions, theories and techniques underpinning qualitative and qualitative research methodologies and evaluate the usefulness for specific problems or foci of study.

I was also equipped with the right resources to reflect, compare and critically analyze the concepts of quantitative designs including observational, analytical and experimental, and evaluate the usefulness for specific types of research question. Prior to that, my basic research skills particularly my research methodology and statistical skills were inadequate for the magnitude of research work I was going to encounter, in my opinion when I enrolled for the doctorate programme. Research by Percy & Beaumont (2008) indicates that reflection is an important element of situational awareness. I was able to acquire sound judgement (interpretation of ideas), effective decision making (from the interpretation formulate a conclusion), self-evaluation (being aware that one's own judgement is professionally suitable) and situational awareness (appreciate the consequences of calculated judgement). These are usually the product of extensive practical experience, defined as clinical competency and expertise

acquired via experiential learning.

Approaches and evaluation strategies for developing and or selecting tools for collecting and analyzing data on health or social phenomena were easier to explain with the completion of the modules. It was now possible to categorize data or foci of study, justify and apply suitable analytical techniques and use a systematic approach to critically appraise the methodology and methods and interpret the results of published accounts of qualitative and/or quantitative research. On the final part of the module, I still needed a lot of clarification involving the articulation of the implications of the contemporary criteria for good 'good research practice' on research planning and employment of strategies to ensure that research fulfils the requirements of clinical, ethical, and research frameworks of hosting organisation and society (Alreck & Settle, 2004).

I attended seminars and symposia to improve my knowledge base and this provided an opportunity for cross-fertilization of ideas and opinions from colleagues and professionals from different backgrounds.

On reflection, my research skills on statistics and methodology were properly developed during my taught modules. And since then, I confidently can subject myself to research with the intention of accomplishing them to the UK academic and scientific standard.

7.4.4 Part 2- reflection on research module

The learning outcomes on the research module are summarized in the following seven paragraphs below.

The first was to conduct ethical research in a complex, multidisciplinary environment. The doctoral level research is complex, challenging and tasking. Developing the methodology for the study was not an easy task coupled with the rigorous process of getting ethical approval from two academic institutions, AECC Bournemouth and University of Portsmouth. Harnessing the available resources before me with the daunting challenge of designing a study for an area that has

very few references in literature was difficult to come to terms with. The final results were fulfilling to me as this was the best I could achieve in the circumstances. It can, at least, serve as a stepping stone to newer researchers in the field.

Secondly, to attain command of the latest knowledge and understanding appropriate to area of professional or educational practice. One of the objectives of this research was to conduct a literature review to ascertain the efficacy of previous studies using sonoelastography. I read quite extensively from conventional ultrasound to elastography and sonoelastography, pathophysiology and pathoetiology of tendinopathy and musculoskeletal injuries, and pain, physics and instrumentation of elasticity. This was a daunting task and coupled with the task of trying to contain everything within the specified word limit. Though I used search engines at random to assist me, on reflection I should have used a mind mapping of all that I needed with planned timing in order to achieve set goals. Going forward, this will help me in estimating the sum of any research work and set to accomplish it within set timeline.

The third was to demonstrate independent critical judgment of complex issues and situations. Using the collected data on strain ratio was a bit complex as it was not clear initially what it would amount to. I had the dilemma of getting a second reference standard for my study and it was unexpected what I finally arrived at. On deliberations, I had to come up with a complex ROC curve to solve this quandary to provide the missing reference standard. This was quite unique because it has never been used and would represent a new index for comparison. On reflection I feel it was the right thing to do given the circumstances and the impossibility of using histology which is invasive as reference standard. Also, the subsequent findings provided for the first time in any published study the strain ratio to estimate the cut-off point for supraspinatus tendinopathy.

Fourthly, make a major and original contribution to professional and educational practice. To make a major and original contribution with this research was really what I set out to do when I enrolled on the professional doctorate programme. The main role of this research was to assess the clinical value of

sonoelastography in patients presenting with symptoms of tendinopathy in the supraspinatus tendon and compare sonoelastography and conventional ultrasound using colour mapping and strain ratio values. This assessed both visual and quantitative parameters that indicate tendinopathy. The study provided evidence to prove early and increased accuracy in the detection of tendinopathy. This should lead to improved patient care in shoulder pathologies. It is hoped other researches will follow in this footsteps to provide more evidence based studies. On reflection I feel fulfilled and believe that I have accomplished the purpose of being a skilled researcher and competent practitioner.

The next was to challenge current thinking and offer authoritative solutions to practical and research problems. I do not hesitate to say that this study challenges current thinking with the authoritative results originating from it. It is held in many quarters that MRI is the gold standard for diagnosing tendinopathy. However, this is disputed as literature has shown that ultrasound is the preferred reference standard. This study has shown the superiority of sonoelastography to conventional ultrasound due to its ability to measure and image tissue elasticity. More so, strain ratio which is a quantitative measure gives additional information on the nature of tissues with a view to revealing what might not be seen on MRI and conventional ultrasound. On reflection I feel the technique of sonoelastography should be made more routine adjunct to all qualified practitioners of musculoskeletal ultrasound and incorporated into the triage for diagnosis of tendinopathy in shoulder scans. It is also impressive that many manufacturers of ultrasound machine are incorporating the software in their products.

The sixth outcome was to manage and make effective use of the appropriate physical, financial and human resources available. One major limitation and discouragement of this research was in terms of collecting data. I had to travel 250 miles each time I went to Bournemouth to collect a set of data almost on a weekly basis for nearly two years. This was a huge aspect of funding that was underestimated but personally borne. I could not get any funding due to limitation of being an international student. I also could not get funding from the manufacturer of the ultrasound machine used due to certain company policies.

However, the AECC Bournemouth provided the site, ultrasound machine, volunteers and patients for the study for which I am grateful. On reflection, I probably could have sought other avenues of funding. I do hope that future researchers will be able to get funding as this is an emerging area in musculoskeletal imaging.

Lastly, use a variety of formats to disseminate theoretical, research and professional understanding to critical communities. The results of this study will be disseminated to the critical communities in numerous ways. An aspect of this thesis was presented at the British Medical Ultrasound Society Conference at The Sage Gateshead United Kingdom in December 9 – 11, 2013. This has kick-started the dissemination of this study to the radiological and musculoskeletal imaging community. The same abstract has been sent to United Kingdom Radiological Congress and International Society for Musculoskeletal Imaging for Rheumatology. Another aspect of the study findings has been sent to the BMUS 2014 edition and awaits approval. The findings of this study will be published as papers in peer reviewed Radiological and Imaging journals and journals of sports medicine in 2014.

7.5 Reflections on my own learning and personal development

The first reflection is on learning achieved within a framework of advanced professional practice. I feel confident to say that I have achieved a great deal of learning having gone through the professional doctorate programme. The learning acquired has equipped me to be a better researcher and advanced practitioner. My overall knowledge, articulation and understanding have significantly increased. When I enrolled on the professional doctorate course, I knew how much I could boast of research knowledge. I felt I was well equipped for the challenges ahead of me both clinically and professionally. On reflection I can now say that I was not. Having gone through the taught modules provided in the program, I am now better equipped in the area of research methodology and statistics, reading, understanding and critiquing of published articles. I have gained great insight into writing and publishing papers with good confidence, and

have also improved with my art of paper presentations. These are things I could not boast of before embarking on the doctorate course. In hind sight, I am very fortunate to have been counselled and guided by Dr Budgie Hussain when I decided to go through the Professional Doctorate pathway instead of PhD. It is likely that I may have struggled and probably taken a longer period to achieve with a PhD what I have done via the Professional Doctorate pathway. I enjoyed all the assistance from Professor Graham Mills and my supervisory team (Dr Alan Castle, Dr Jason Oakley, Dr Penny Delf, Dr Kieron Hatton and Dr Budgie Hussain), and more so, the enhanced team work and partnership with my cohorts (the Bumble Bees).

The second reflection is on influence and inspiration provided, and leadership for others in a changing environment of healthcare education or professional practice. Reflecting on the inspiration and leadership role in our changing healthcare education and professional practice, I can only but feel elated to mention a few. Musculoskeletal ultrasound is an area of interest I felt I could go all the way to the top. I completed an MSc in Musculoskeletal Ultrasound and went on to strive to gain a doctorate. Since then, I have had no fewer than modest eighteen publications with associates in peer reviewed journals, and a few more in press. I have mentored and clinically supervised three students who graduated with post graduate diploma in medical ultrasound and musculoskeletal ultrasound, and one that graduated with an MSc in Musculoskeletal Ultrasound. I am currently supervising two more in MSc Musculoskeletal Ultrasound. I was also appointed Honorary lecturer and researcher at the Centre for Ultrasound Studies, Anglo European College of Chiropractic, Bournemouth (January 2011 till date). I have been a journal reviewer of the South African Journal of Radiography Johannesburg, South Africa (2010-2013). I was also appointed an editorial board member of X-Ray, Journal of Radiography & Radiological Sciences (Association of Radiographers Nigeria, 2012 – Present). I have an on-going opportunity to be appointed a consultant sonographer in the NHS where I can inspire and provide cognitive, practical, professional and transferable skills to younger practitioners to improve practice and enable them assume more active roles within their professional field.

7.6 Conclusion

In conclusion, I can look back and say that it has been a titanic journey for me. My goal has been to come up with a scientifically based research that would impact positively on diagnostic imaging. Reflecting on the gains of the professional doctorate programme, I can say that it can only get better. Having already personally achieved so much in terms of academic exposure and clinical improvement, I intend to continue my next phase of learning by looking at the use of sonoelastography in other tendons in the body and other soft tissue pathologies where elasticity and compressibility are evident. The findings of the study will also be disseminated through the right channel to target audiences. I intend working together with sports physicians to assess the impact of sonoelastography on muscle-tendon exercise and function. I also would like to work with rheumatologists and ascertain if sonoelastography could provide early synovitic detection in suspected cases of active synovitis in rheumatological disorders.

I am frankly grateful to all those that were instrumental to this milestone in my life, and as many as taught me at the University of Portsmouth during my period of study on the professional doctorate programme.

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Appendix A CASP Tool

Three broad issues need to be considered when appraising a diagnostic test:

Are the results of the study valid? (Section A)

What are the results? (Section B)

Will the results help me and my patients/population? (Section C)

A summary of the CASP criteria used are listed below:

(A) Are the results of the study valid?

1. Was there a clear question for the study to address?
2. Was there a comparison with an appropriate reference standard?

Is it worth continuing?

3. Did all patients get the diagnostic test and reference standard?
4. Could the results of the test have been influenced by the results of the reference standard?
5. Is the disease status of the tested population clearly described?
6. Were the methods for performing the test described in sufficient detail?

(B) If so, what are the results?

7. What are the results?
8. How sure are we about the results? Consequences and cost of alternatives performed?

(C) Will the results help me and my patients/population?

9. Can the results be applied to your patients/the population of interest?
10. Can the test be applied to your patient or population of interest?
11. Were all outcomes important to the individual or population considered?
12. What would be the impact of using this test on your patients/population?

Appendix B STARD Document

Section & Topic	Item#		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	
	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
METHOD			
<i>Participants</i>	3	Describe the study population: The inclusion and exclusion criteria, setting and locations where the data were collected.	
	4	Describe participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Describe participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected.	
	6	Describe data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
<i>Test methods</i>	7	Describe the reference standard and its rationale.	
	8	Describe technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	
	9	Describe definition of and rationale for the units, cutoffs and/or categories of the results of the index tests and the reference standard.	
	10	Describe the number, training and expertise of the persons executing and reading the index tests and the reference standard.	
	11	Describe whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	
<i>Statistical methods</i>	12	Describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	
	13	Describe methods for calculating test reproducibility, if done.	
RESULTS			
	14	Report when study was done, including beginning and ending dates of recruitment.	
	15	Report clinical and demographic characteristics of the study population (e.g. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centres).	
	16	Report the number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended).	
<i>Test results</i>	17	Report time interval from the index tests to the reference standard, and any treatment administered between.	
	18	Report distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	
	19	Report a cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	
	20	Report any adverse events from performing the index tests or the reference standard.	
<i>Estimates</i>	21	Report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	
	22	Report how indeterminate results, missing responses and outliers of the index tests were handled.	
	23	Report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if done.	
	24	Report estimates of test reproducibility, if done.	
DISCUSSION	25	Discuss the clinical applicability of the study findings.	

Appendix C QUADAS 2

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Appendix D Participant Information Sheet (For Volunteer)



PARTICIPANT INFORMATION SHEET (FOR VOLUNTEER)

Project Title: Measurement of Supraspinatus Tendon Strain Ratio with Sonoelastography: An Exploratory Study

You are being invited to participate in a research study. Before you decide on whether to take part it is important for you to understand the nature and purpose of the research. Please take time to read this information sheet carefully as it explains the purpose of the research and what happens if you participate. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The aim of the study is to assess how accurate the use of colour image ultrasound (sonoelastography) is in determining the degree of tendon damage in patients presenting with shoulder pain. The intention is to use this colour imaging technique called sonoelastography to improve diagnosis.

Why have I been chosen?

You have been chosen because you volunteered to have your shoulder scanned. We are interested in seeing what your shoulder looks like on grey and colour image. We are looking forward to see nearly 200 other volunteers.

Do I have to take part?

No. It is your choice to decide whether or not to take part in the study. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. Declining will not in any way affect your investigation going on and the result passed on to your referrer (routine care).

What will happen to me if I take part?

The principal researcher will carry out an ultrasound investigation of the shoulder. It involves exposing only the shoulder and the use of gel on the skin. The examination is safe and is not harmful (does not involve the use of radiation). It will last about 15-20 minutes. You will also see the pictures on the screen as the investigation is done.

Will my taking part in the study be kept confidential?

Yes. All the information about your taking part in the study will be kept confidential. The images and report of your investigation will be coded, anonymised and securely stored in a computer that is password protected. All data collected will be deleted from the ultrasound machine / computer after the completion of the study.

What will happen to the results of the research study?

The results of the study may be presented at seminars, conferences and/or published. No individual will be identifiable in the images and reports as they will be coded. You may be informed of the results of the study if you wish.

Who is organising and funding the research?

The principal researcher Chyke Ohuegbe is undertaking this research project in his role at the Centre for Ultrasound, Anglo European College of Chiropractic (AECC) Bournemouth. The other research team member is Dr Jane Cook, a chiropractor and musculoskeletal sonographer. The costs of this study have been met through the principal researcher. (14c)

Who has reviewed this study?

The study has been approved by the University of Portsmouth and AECC Bournemouth Research Ethics Committee.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. This can be directed to the contact below.

For further information and advice on any aspect of the ultrasound procedure, this can be directed to:

Dr Budgie Hussain

Director, Centre for Ultrasound Studies, AECC Bournemouth

Tel: 01202436211

Thank you for taking the time to read this information sheet and considering participating in the research study. You will be given a copy of this information sheet along with a copy of the signed consent form to keep.

When completed, 1 for participant, 1 (original) for research site file.

Appendix E Participant Information Sheet (For Patient)



PARTICIPANT INFORMATION SHEET (FOR PATIENT)

Project Title: Measurement of Supraspinatus Tendon Strain Ratio with Sonoelastography: An Exploratory Study

You are being invited to participate in a research study. Before you decide on whether to take part it is important for you to understand the nature and purpose of the research. Please take time to read this information sheet carefully as it explains the purpose of the research and what happens if you participate. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study? The aim of the study is to assess how accurate the use of colour image ultrasound (sonoelastography) is in determining the degree of tendon damage in patients presenting with shoulder pain. The intention is to use this colour imaging technique called sonoelastography to improve diagnosis.

Why have I been chosen?

You have been chosen because you were sent by your referrer/doctor to have your shoulder scanned here. We are interested in seeing what is happening to your shoulder.

Do I have to take part?

No. It is your choice to decide whether or not to take part in the study. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

The principal researcher will carry out an ultrasound investigation of the affected shoulder. It involves exposing only the shoulder and the use of gel on the skin. The examination is safe and is not harmful (does not involve the use of radiation). It will last about 15-20 minutes. You will also see the pictures on the screen as the investigation is done.

What will happen to me if I do not take part?

Declining will not in any way affect your investigation going on and the result passed on to your referrer.

Will my taking part in the study be kept confidential?

Yes. All the information about your taking part in the study will be kept confidential. The images and report of your investigation will be coded, anonymised and securely stored in a computer that is password protected. All data collected will be deleted from the ultrasound machine / computer after the completion of the study.

What will happen to the results of the research study?

The results of the study may be presented at seminars, conferences and/or published. No individual will be identifiable in the images and reports as they will be coded. You may be informed of the results of the study if you wish.

Who is organising and funding the research?

The principal researcher Chyke Ohuegbe is undertaking this research project in his role at the Centre for Ultrasound, Anglo European College of Chiropractic (AECC) Bournemouth. The other research team member is Dr Jane Cook, a chiropractor and musculoskeletal sonographer. The costs of this study have been met through the principal researcher.

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Director, Centre for Ultrasound Studies, AECC Bournemouth

Tel: 01202436211

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When completed, 1 for participant, 1 (original) for research site file.

Appendix F Consent Form



Consent Form

Project Title: Measurement of Supraspinatus Tendon Strain Ratio with Sonoelastography: An Exploratory Study

Name of Researcher: Chyke Ohuegbe

Please initial box

1. I confirm that I have read the information sheet dated..... for the above study.
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free
to withdraw at any time without giving a reason.

3. I agree to take part in the above study

.....

.....

.....

Name of Participant

Date

Signature

.....

.....

.....

Name of Researcher

Date

Signature

(Or Person taking consent if different from Researcher)

Please use my contact details below if you would like more information about this research study.

Chyke Ohuegbe

PO Box 1100

Luton. LU2 7QS

Email: ihchio@yahoo.com

Tel Mobile: 07405967641

Tel Home: 01582 453199

When completed, 1 for participant, 1 (original) for research site file.

Appendix G Raw Data for ROC Curve

Coordinates of the Curve

Test Result Variable(s): SR

Positive if Greater Than or Equal To ^a	Sensitivity	1 - Specificity
-.1000	1.000	1.000
1.0000	1.000	.979
1.1500	1.000	.969
1.3000	1.000	.958
1.4500	1.000	.938
1.6500	1.000	.927
1.8500	1.000	.885
1.9500	1.000	.844
2.0500	1.000	.802
2.1500	1.000	.781
2.2500	1.000	.771
2.3500	1.000	.760
2.4500	1.000	.740
2.5500	1.000	.698
2.6500	1.000	.646
2.7500	1.000	.625
2.8500	1.000	.552
2.9500	1.000	.531
3.0500	1.000	.510
3.1500	1.000	.385
3.2500	1.000	.313
3.3500	1.000	.271
3.4500	1.000	.229
3.5500	1.000	.219
3.7000	.991	.198
3.8500	.991	.188
3.9500	.981	.156
4.0500	.981	.146
4.1500	.972	.135
4.2500	.963	.135
4.3500	.944	.125
4.4500	.935	.125
4.5500	.907	.115
4.6500	.889	.115
4.7500	.843	.104
4.8500	.806	.083
4.9500	.796	.083
5.0500	.778	.083

5.1500	.759	.083
5.2500	.750	.083
5.3500	.713	.063
5.4500	.667	.063
5.5500	.657	.063
5.6500	.648	.063
5.7500	.630	.063
5.8500	.593	.063
5.9500	.574	.042
6.0500	.537	.042
6.1500	.481	.042
6.2500	.444	.042
6.3500	.426	.042
6.4500	.333	.031
6.5500	.287	.031
6.6500	.231	.031
6.7500	.204	.031
6.8500	.194	.031
6.9500	.185	.031
7.0500	.176	.031
7.2500	.167	.031
7.5000	.157	.021
7.6500	.148	.021
7.7500	.148	.010
7.8500	.120	.010
7.9500	.111	.010
8.0500	.093	.010
8.1500	.083	.010
8.2500	.074	.010
8.3500	.065	.010
8.4500	.056	.010
8.6500	.046	.010
9.1000	.037	.010
9.7500	.028	.010
11.9500	.019	.010
20.7500	.009	.010
39.9500	.000	.010
53.2000	.000	.000

The test result variable(s): SR has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Appendix H Literature Summary of Tendon studies using Sonoelastography

Authors/Year	Study Objective	Sample size	Equipment	Results /Recommendations
1. Klauser et al, 2006	To assess Achilles tendons, paratenon and bursae in healthy volunteers and to compare the findings with patients complaining of achillodynia with real-time sonoelastography.	15 patients with 18 painful Achilles tendons and 18 tendons in sex and age matched healthy volunteers	Hitachi EUP-8500, L54M, 6-13 MHz probe	In all patients a significant higher detection of intratendinous colour alterations was detected by sonoelastography (green, yellow, red) in comparison to gray scale US ($P < 0.001$). Comparison to healthy volunteers showed significant differences for tendon stiffness ($P < 0.0001$). Detection of tendon thickening, partial tears and peritendinous alterations showed a good correlation with gray scale US ($P < 0.001$).
2. De Zordo et al, 2007a	To assess Achilles tendons in healthy volunteers and patients with achillodynia by using Sonoelastography (SEL) compared to B-mode Ultrasound (US) and MRI. Interobserver variability was calculated.	50 Achilles tendons in 25 consecutive patients with unilateral complains and 50 Achilles tendons in 25 healthy sex age matched volunteers were examined. 22/25 patients underwent MRI.	Hitachi EUP-8500, L54M, 6-13 MHz probe	SEL of healthy volunteers showed no Grade 3, but Grade 2 was found in 16% at mid-portion and in 4% at proximal tendon thirds. Patients showed Grade 3 in 64% (16/25) of the distal part, in 80% (20/25) of the mid-portion, and 28% (7/25) of the proximal part. SEL showed good correlation with US ($P < 0.001$, $R = 0.864$) and MRI ($P < 0.001$, $R = 0.844$). Asymptomatic contralateral side of patients showed an overall statistical significant difference ($P < 0.001$) compared to healthy volunteers, located in the middle third by using both US ($P < 0.001$) and SEL ($P < 0.001$), for SEL alone in the distal part ($p < 0.001$). Good Interobserver variability was found (2.9%). SEL detected sensitively alterations in symptomatic Achilles tendons and showed excellent correlation with MRI and US. SEL was more sensitive in detection of subclinical alterations
3. De Zordo et al, 2007b	To assess extensor tendon insertion of the elbow in healthy volunteers and to compare the findings with patients complaining of lateral epicondylitis with real-time sonoelastography.	15 consecutive patients and 15 sex and age matched healthy volunteers by using RTSE and compared it to findings in gray scale sonography	Hitachi EUP-8500, L54M, 6-13 MHz probe	Elbow extensor tendon insertion in healthy volunteers showed all blue to green coloring consistent with stiff normal tendon tissue and normal findings at gray scale US. In all patients extensor tendon insertion showed a significant higher detection of intratendinous color alterations detected by sonoelastography (yellow, red) in comparison to focal lesion detection by using gray scale US ($P < 0.001$) only. Comparison to healthy volunteers showed significant differences for tendon stiffness ($P < 0.0001$). Furthermore decreased differentiation of overlying soft tissue structures was found in patients compared to healthy volunteers ($P < 0.001$).
4. Abdel Razek & Ezzat, 2008	To assess real-time ultrasound elastography for evaluating the supraspinatus tendons of healthy volunteers patients presenting with	Studying 20 healthy volunteers and 40 patients presenting with shoulder pain.	Hitachi EUB-7500, L54M, 7.5-13 MHz probe	In the 20 healthy volunteers, elastography showed blue colour throughout the tendon, which is consistent with stiff normal tendon tissue and normal findings at grayscale, Razek said. In the patients with partial tears, elastography showed intratendinous colour

	<p>shoulder pain. The elastography findings were then compared with the B-mode results, and for 20 patients, elastography was also compared with MRI findings. Arthroscopy was performed only when elastography was positive and MRI had a negative finding.</p>			<p>alterations (green, yellow, and red) not reaching the bursal or articular aspects. Patients with full tears showed colour alterations reaching the bursal or articular surfaces.</p> <p>The differences in tendon stiffness between the healthy volunteers and the patients were statistically significant ($p < 0.0001$). The elastography and MRI findings also showed good correlation ($p < 0.001$).</p> <p>In addition, elastography was able to diagnose tendinitis and mild synovial effusion in four cases (10%) that had false-negative findings on MRI. Elastography changed the diagnosis of partial tear into complete tear in two cases (5%), Razek said. "The sensitivity and negative predictive value has been increased from 95% to 97% and from 87% to 93% by adding elastography to the conventional ultrasound technique."</p> <p>Elastography can also be used as an easy reproducible follow-up method to monitor treatment.</p>
5. De Zordo et al, 2009	<p>To evaluate Sonoelastography (SEL) in the assessment of common extensor tendon origins in healthy volunteers and patients complaining of lateral epicondylitis and compare these findings to clinical examination, and Ultrasound (US) findings. Correlation to Power Doppler Ultrasound (PDUS) and pain score, using a visual analog scale (VAS), was performed. Clinical examination was used as standard of reference.</p>	<p>In a prospective analysis 38 elbows of 32 consecutive patients (10 men, 22 women; mean age, 52.63 years; range, 38-70 years) complaining of lateral epicondylitis and 44 asymptomatic elbows of 28 healthy volunteers (11 men, 17 women; mean age, 43.64 years; range, 24 - 89 years) were assessed by clinical examination, US, PDUS and SEL.</p>	Hitachi EUP-8500, L54M, 6-13 MHz probe	<p>In healthy volunteers, real-time sonoelastographic images showed hard tendon structures in 96% of tendon thirds and mild alterations in 4%. Real-time sonoelastography of patients showed hard structures in 33% of tendon thirds but softening of different grades in 67%, a statistically significant difference in relation to the findings in healthy volunteers ($p < 0.001$). Using SEL a sensitivity of 100%, a specificity of 89%, an accuracy of 94%, a positive predictive value of 88% and a negative predictive value of 100% was found, whereas US showed a sensitivity of 95%, a specificity of 89%, an accuracy of 91%, a positive predictive value of 88% and a negative predictive value of 95%. SEL showed good correlation to US findings ($R > .900$). No correlation between US and PDUS or SEL and PDUS could be detected, but PDUS showed a strong correlation with VAS score.</p>
6. De Zordo et al, 2008	<p>To evaluate Sonoelastography (SEL) in Achilles tendon assessment compared to clinical examination and conventional Ultrasound (US) of consecutive</p>	<p>Achilles tendons of 25 consecutive patients (11 men, 14 women; mean age, 55 years;</p>	Hitachi EUP-8500, L54M, 6-13 MHz probe	<p>In healthy volunteers, normal findings were present in 100% of clinical examinations, in 100% of US images and in 93% of SEL images. In patients, alterations were found in 61% of clinical examinations, in 59% of US images and in 68% of SEL images. SEL showed a sensitivity of 94%, specificity of 99%, and accuracy of 97%, while US</p>

	<p>patients with chronic Achilles tendinopathy healthy volunteers. Examined by clinical examination, US, and SEL, by assessing the proximal-, middle- and distal third. By using US, tendon thickening and/or intratendinous focal areas were defined as pathologic and by using SEL tissue softening was defined as pathologic. Contralateral tendons were assessed separately.</p>	<p>range, 37-79 years) and 25 healthy volunteers (11 men, 14 women; mean age, 46 years; range 25-76 years).</p>		<p>showed a sensitivity of 93%, specificity of 100% and accuracy of 99%. Correlation (κ) between SEL and US was 0.89. Furthermore, asymptomatic contralateral tendons of patients showed a more common involvement by using SEL (16 patients) when compared to US (13 patients). Detection of tissue softening could add knowledge regarding early development of Achilles tendinopathy, which might have an impact on therapeutic decisions.</p>
7. Klauser et al, 2009a	<p>We investigated the performance of RTSE in the detection of Achilles tendinopathy and</p>	<p>We examined 80 Achilles tendons in healthy volunteers and 25 tendons in patients complaining of inflammation and pain in the Achilles region (achillodynia).</p>	<p>We used an Hitachi EUB-8500 for the Achilles tendon. 6-13 MHz probe.</p>	<p>Alterations were most often observed in the midportion of the Achilles tendon (80%). RTSE had a mean sensitivity of 94%, specificity of 99%, and accuracy of 97% when compared with clinical examination. A strong correlation was found with conventional ultra sound findings ($r = 0.89$).</p>
8. Klauser et al, 2009b	<p>We investigated the performance of RTSE in the detection of lateral epicondylitis (tennis elbow).</p>	<p>38 elbows from patients with clinically suspected tennis elbow and 44 asymptomatic elbows.</p>	<p>Hitachi EUB-9000 for the elbow. 6-13 MHz probe</p>	<p>RTSE also detected lateral collateral ligament and overlaying fascia involvement. Comparison with clinical examination as the reference standard showed RTSE to have a sensitivity of 100%, specificity of 89%, and accuracy of 94%. Correlation with ultrasound findings was good once again ($r = 0.900$).</p>

Appendix I Modified classification for staging tendinopathy

Clinical and functional classification for tendinopathy involving four stages was proposed by Blazina et al, (1973). This was followed by a classification system in three stages by Neer and Welsh (1977). Another classification in three stages involves the chronology of symptoms by Kaux, Forthomme, Le Goff, Crielaard, Croisier (2011). Bringing all these classifications together, the author adapted these existing classifications that resulted in a modified classification for this research.

A. Clinical and functional classification for tendinopathy as proposed by Blazina et al, (1973).

Four stages are seen.

- Stage 1 -pain after sports activity;
- Stage2 - pain at the beginning of sports activity, disappearing with warm-up and sometimes reappearing with fatigue;
- Stage 3 - pain at rest and during activity;
- Stage 4 - rupture of the tendon.

B. Neer and Welsh (1977) proposed a classification system for shoulder tendinopathy as follows:

- Stage I, mostly seen before the age of 25, consists of oedema and haemorrhage of the supraspinatus and biceps tendons from overuse.
- Stage II consists of fibrosis and tendinitis, and usually occurs in those older than 25 years.
- In Stage III, seen mostly after 40 years of age, there is degeneration and rupture of the tendons, as well as changes in the bony structure (Neer and Welsh, 1977).

C. The chronology of symptoms was also classified into 3 stages- (Kaux, Forthomme, Le Goff, Crielaard, Croisier (2011).

- Stage 1- when symptoms have been present for 0 to 6 weeks, the tendinopathy is characterized as “acute”;
- Stage 2 - between 6 to 12 weeks, it is regarded as “sub-acute”;
- Stage 3 - after more than 3 months, it may be considered as “chronic”

D. Modified classification of Kaux et al (2011) irrespective of age of patient– used for the study (2014)

The chronology of symptoms was also classified into 3 stages:

- Stage 1- symptoms present for 0 to 6 weeks, the tendinopathy is characterized as “acute”;
- Stage 2 – symptoms between 6 to 12 weeks, regarded as “sub-acute”;
- Stage 3 - after more than 3 months, it may be considered as “chronic”.

Appendix J Architectural display of Phase III research question

Table Architectural display of Phase III research question.

		Target disorder (SS tendinopathy)		Totals
		Patient with tendinopathy on US (present)	Patient without tendinopathy on US (absent)	
Diagnostic test result (SE)	Positive strain ratio (<4.0)	a(TP)	b(FP)	(a+b)
	Negative strain ratio (>4.0)	c(FN)	d(TN)	(c+d)
Totals		(a+c)	(b+d)	a+b+c+d)

Key: TP= True Positive, TN= True Negative, FP= False Positive, FN= False Negative

Sensitivity = $a/(a+c)$; Specificity = $d/(b+d)$, positive likelihood ratio (LR+) = Sensitivity/ 1 – specificity, and negative likelihood ratio (LR-) = 1 – sensitivity/ specificity. Medcalc diagnostic test calculator is used to calculate the values with the accompanying confidence intervals.

Appendix K Raw data for strain ratio sonoelastography grading for all the phases of the study